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The American Journal of Medicine

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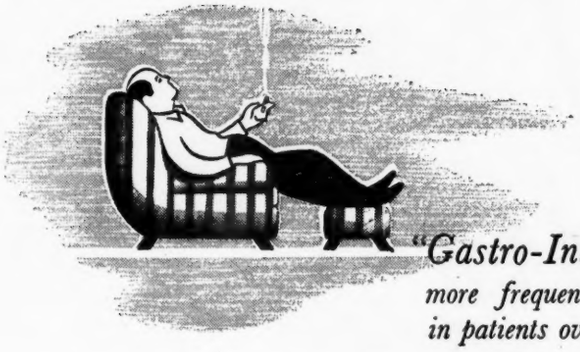

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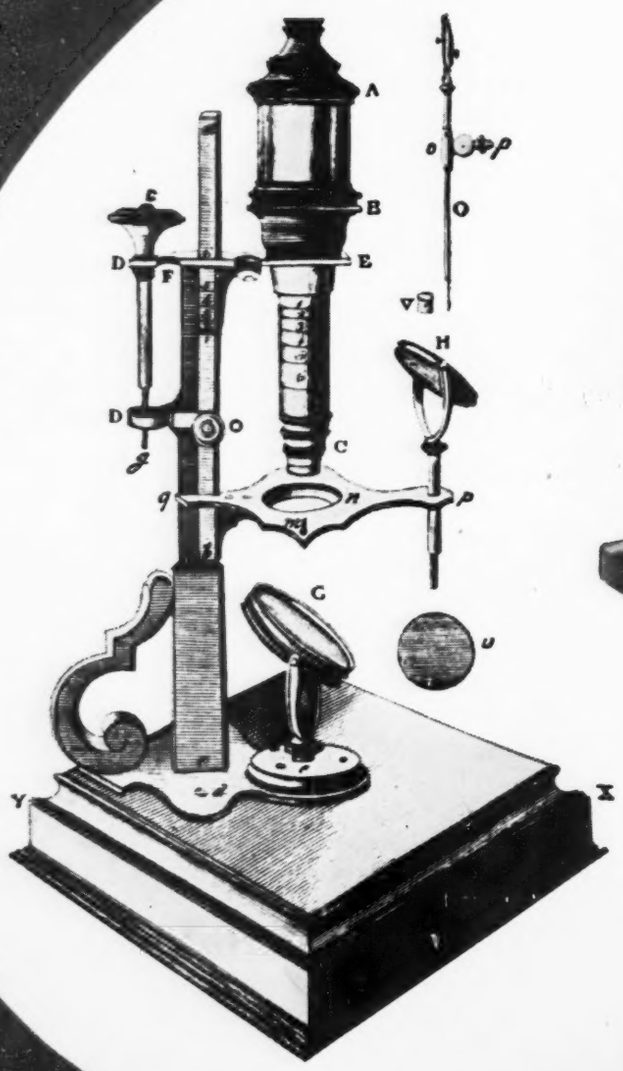

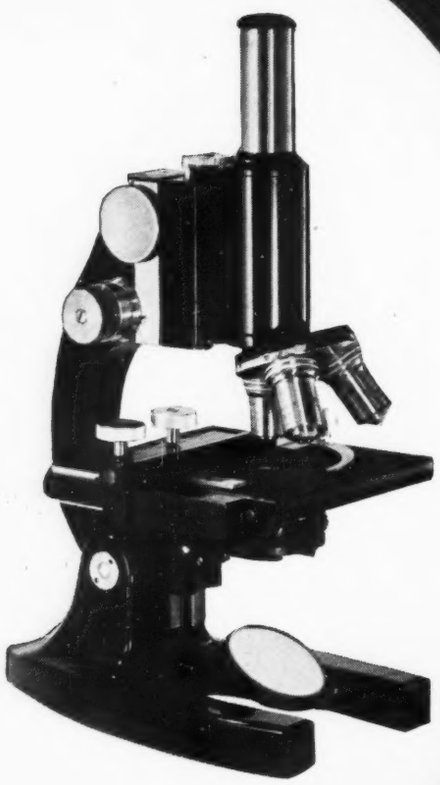

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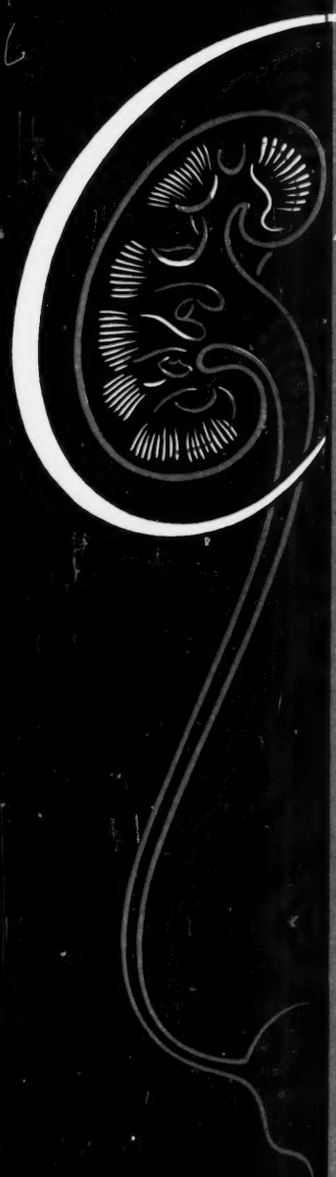

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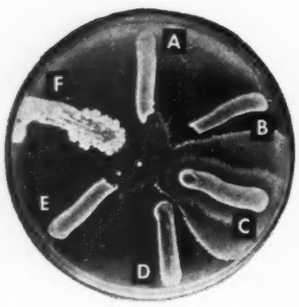

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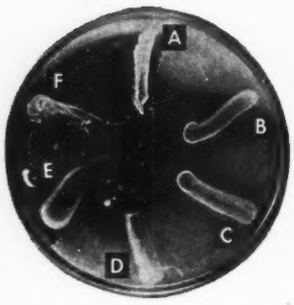

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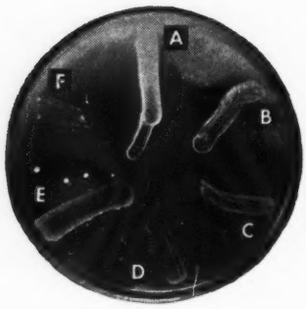

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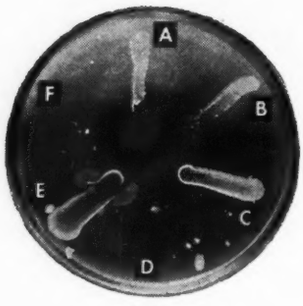
Antibacterial Activity of STREPTOMYCIN

KEY TO PHOTOGRAPHS: • A. *Escherichia coli*
B. *Eberthella typhosa* • C. *B. proteus* • D. *Klebsiella pneumoniae*
E. *Bacillus pyocyaneus* • F. *Mycobacterium tuberculosis*
The numerals indicate micrograms of Streptomycin per cc. of agar.



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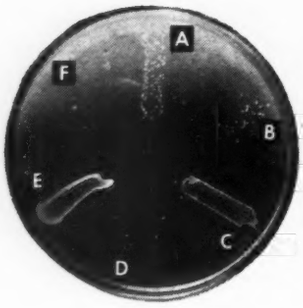

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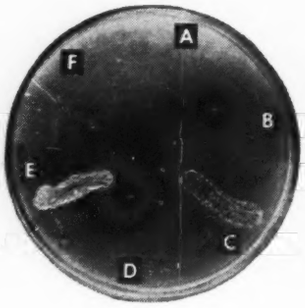

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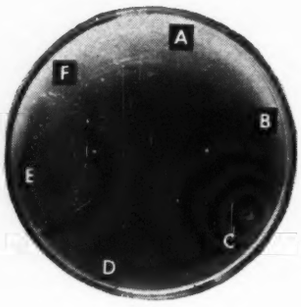

104.

THESE photographs show the inhibitory action of increasing concentrations of Streptomycin on a strain of six representative organisms *in vitro*. Inhibitory levels of concentration vary significantly with different strains.

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The American Journal of Medicine

VOL. 1 SEPTEMBER, 1946 NO. 3

The Anticonvulsant Properties of Tridione*

Laboratory and Clinical Investigations

LOUIS S. GOODMAN, M.D., JAMES E. P. TOMAN, PH.D. *and* EWART A. SWINYARD, M.S.†
With the technical assistance of Corinne Manuel, Marshal Merkin and Mary Murata
SALT LAKE CITY, UTAH

TRIDIONE, 3,5,5-trimethyloxazolidine-2, 4-dione, has recently been made available to physicians as a specific symptomatic therapy for petit mal epilepsy, and has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in New and Nonofficial Remedies. The drug was synthesized by Spielman[31] and initially studied and reported as an analgesic agent.[26,28] Its pharmacological and anticonvulsant properties were described by Richards and Everett[8,26,27,28] and by us.[13,14,15,17,18,34,35,38,42,43] The earliest observations on the specificity of Tridione in petit mal were made by Perlstein,[29] and the most extensive clinical studies to date are those of Lennox.[21,22] The field of usefulness of Tridione has also been extended to psychomotor epilepsy.[5,24,29] Available evidence indicates that Tridione offers no advantage in the treatment of grand mal.[22,24,27,36] Preliminary observations have been made on its use in tetanus and status epilepticus,[7,24,27,29,36] in athetoses and in behavior disturbances in children.[24,29]

The following report is concerned with the laboratory analysis of Tridione* in comparison with other anticonvulsant drugs, and with the clinical results obtained in a selected group of patients with slow wave EEG dysrhythmias, particular attention being paid to the EEG criteria for the use of Tridione alone or in combination with other agents. This study is part of a program concerned with properties of experimental and clinical convulsive disorders and their therapy. Tridione has received particular attention because elucidation of its mechanism of action in petit mal can yield considerable information on the nature of this disorder. New experimental methods reported here for analysis of anticonvulsant drugs may provide the basis for the discovery of agents which have higher therapeutic indices or greater specificity of action.

TECHNICS AND MATERIAL

I. LABORATORY STUDIES. The following six laboratory indices were used for the analysis of Tridione and its comparison with

* Generously supplied by Dr. R. K. Richards, Abbott Laboratories, North Chicago, Illinois.

* From the Departments of Pharmacology and Physiology, University of Utah School of Medicine, Salt Lake City, Utah. Grateful acknowledgment for financial assistance is made to the Research Fund, University of Utah School of Medicine, and to The Abbott Laboratories, North Chicago, Illinois.

† Winthrop Research Fellow, Department of Pharmacology, University of Utah School of Medicine.

other agents. The first two are commonly accepted laboratory tests for the detection and assay of anticonvulsant drugs. The remaining four technics were devised in our laboratory to provide the basis for a more adequate comparison of such agents.

1. *Prevention of Metrazol Convulsions.* A standard convulsant dose (CD_{95}) of metrazol was determined for populations of mice and rats, and the convulsant dose of metrazol was established in individual cats, rabbits and monkeys. The protective potencies of Tridione and other anticonvulsant drugs were then ascertained.

2. *Elevation of Normal Electroshock Seizure Threshold.* Rats, rabbits, cats and monkeys were used. In most experiments, 60-cycle alternating current (Offner electroshock apparatus) and Spiegel corneal electrodes[30] were employed. Threshold current for fixed duration of stimulus (usually 0.2 sec.) was determined in each individual animal which then served as its own control for the subsequent study of anticonvulsant drugs.

3. *Elevation of Electroshock Threshold in Hydrated Animals.* The effect of Tridione and other anticonvulsants was studied in rats in which the electroshock threshold had been lowered by brain cell hydration resulting from extracellular electrolyte loss. The details of the procedure and the value of the technic as a screening device for anticonvulsant drugs have been described elsewhere.[34]

4. *Modification of the Pattern of Maximal Electroshock Convulsions.* In rats, rabbits and cats the pattern of the seizure elicited by electroshock current intensities several times the threshold was analyzed. The effects of Tridione and other agents on individual components of this pattern were then studied. The details of the technic and its value for the laboratory detection of anticonvulsant drugs have been presented elsewhere.[43]

5. *Modification of Non-convulsive EEG Discharges Induced by Cortical Stimulation.* Rabbits were employed for these experiments. Aseptically implanted epidural electrodes were used for both stimulation and recording. Single condenser shocks were applied to one cerebral hemisphere while records were taken from the other. Thresholds were determined both for contralateral movement and for the various components of the EEG discharge. The effects of Tridione and other drugs on the threshold for and character of these cortically induced discharges were then determined. The details of this technic have been briefly reported.[37,41]

6. *Prevention of Metrazol-induced Petit Mal-like Cerebral Dysrhythmias.* Rabbits with implanted epidural electrodes were used. The amount of metrazol, given either subcutaneously or by slow intravenous infusion, necessary to produce non-convulsive slow wave EEG dysrhythmia was determined both before and after administration of Tridione and other anticonvulsants. Details of the method have been described elsewhere.[38]

II. CLINICAL STUDIES. Eleven patients with clinical histories of seizures and slow wave EEG dysrhythmias were placed on Tridione therapy and followed carefully for a period of six months or longer. Special attention was paid to seizure incidence and character, Tridione toxicity, effect of withdrawal, influence of the drug and its withdrawal on the EEG, and efficacy of combined drug treatment.

RESULTS

I. ANTICONVULSANT EFFECTS IN ANIMALS

1. *Prevention of Metrazol Convulsions.* In previous reports[13,14,15,17,18,38] we have commented on the remarkable pharmacological antagonism between Tridione and metrazol. The quantitative features of this antagonism may be briefly summarized here.

In all species tested (mice, rats, rabbits, cats, monkeys), a dose of Tridione smaller than that required to cause obvious neurological depression is capable of preventing completely all central excitatory effects of a dose of metrazol convulsant in 95 per cent of control animals (CD). Doses of Tridione causing minimal central depression are capable of protecting against approximately two CD'S. When still larger doses of Tridione are employed, several multiples of the CD of metrazol may be injected without evidence of central effects, the quantitative relationship being as follows (rats, rabbits, cats): Protection is afforded against approximately seven CD's of metrazol by each Gm. of Tridione per kg. of body weight. To emphasize the magnitude of this protection, it may be observed that barbiturates in equivalent neurological doses provide only approximately one-half this degree of protection. In single doses, diphenylhydantoin is ineffective against metrazol.[12,16] We have also found that Tridione affords protection against picrotoxin, strychnine, and Coramine (mice, rats, cats), but the antagonism against these convulsants is not as great as that against metrazol.

Cats and rabbits were given equally depressant doses of phenobarbital and Tridione. Their neurological status and EEG's were then continuously examined during and subsequent to injection of metrazol. The Tridione-treated animals could be restored to normal by metrazol, but the phenobarbital-treated animals could not be similarly restored by any amount of metrazol up to and including that producing seizures.

The duration of action of single large doses of Tridione was determined in rats, rabbits, cats and monkeys. Protection against metrazol persisted for more than seventy-two hours. It was found that 30 per cent of the initial protection remained at twenty-four hours (rats, rabbits). The persistence of Tridione action is longer than that of phenobarbital.

2. *Elevation of Normal Electroshock Seizure Threshold.* Monkeys, rabbits, cats and rats were employed for this standard laboratory test. In Table 1 are presented typical data obtained in rats. Tridione and phenobarbital contrast sharply with diphenylhydantoin in that the latter is not able to elevate significantly the normal electroshock threshold. Tridione appears to be somewhat more effective than phenobarbital with respect to this index. The results obtained in monkeys, cats and rabbits paralleled those for rats.

TABLE 1
EFFECT OF ANTI-EPILEPTIC DRUGS ON NORMAL THRESHOLD FOR ELECTROSHOCK SEIZURES IN RATS

Drug	No. of Rats	Dose Mg./Kg. i.p.	Electroshock Threshold* in m.a. (Mean ± S.E.)		Per Cent Increase in Threshold (Mean ± S.E.)
			Initial Control	Threshold after Drug	
Controls	159	...	28±0.29		
Tridione	12	400	28±1.07	36±1.71	28.6±4.08
Phenobarbital	15	45	31±1.61	38±1.58	20.6±3.81
Diphenylhydantoin	10	60	30±2.60	30±2.24	1.7±2.7

* 0.2 sec. stimulus duration.

It has been our consistent experience that anticonvulsant drugs administered in non-depressant doses either do not elevate the normal electroshock threshold (diphenylhydantoin) or do so only to a limited degree (Tridione, phenobarbital).[13–18,33,34,40,43] In no species has it been possible to demonstrate that diphenylhydantoin significantly elevates the threshold for electroshock seizures. This has been found equally true both with 60-cycle alternating current stimulation of brief (0.2 sec.) or long (10 sec.) duration, and with the interrupted direct current method originally described by Putnam and Merritt.[25] Although the

character of the seizures could be modified by diphenylhydantoin, EEG evidence of convulsive discharge and overt evidence of post-ictal depression persisted well beyond the period of stimulation. With the long periods of stimulation customarily used by other investigators, we have consistently found that animals treated with diphenylhydantoin nevertheless exhibit overt seizures during the stimulation period whenever the control electroshock threshold has been exceeded. The effect of the drug is to decrease the total duration of the convulsion during the period of prolonged stimulation rather than to elevate the seizure threshold itself. Such a seizure is masked by the continued passage of the stimulating current and the resulting refractoriness is itself sufficient to leave a true increase of about 100 per cent in seizure threshold when tests are made at five-minute intervals. This explains the apparent increase in threshold found by other investigators who used prolonged stimulation and failed to record seizures unless they persisted beyond the stimulus period.

The above observations and analysis permit the conclusion that agents clinically effective against convulsive disorders need not be capable of elevating normal seizure threshold. It is widely accepted that clinical seizures are due to abnormally lowered thresholds, although such data as are available are not in agreement.[10,19,23] In sharp contrast to the inability of diphenylhydantoin to elevate the normal seizure threshold is its ability to raise the experimentally lowered seizure threshold. On the basis of this and other evidence, it has been suggested by us that this particular drug is clinically effective either by raising abnormally lowered seizure thresholds or by preventing maximal interneuronal facilitation or both.[16,43]

3. *Elevation of Electroshock Threshold Experimentally Lowered by Brain Cell Hydration.* In the course of a study of the influence of brain electrolyte and water distribution on convulsive threshold, the technic of Darrow and Yannet was employed in rats to deplete extracellular electrolyte without loss of total body water. The resulting hydration of brain cells is accompanied by a considerable decrease in threshold for electroshock and metrazol seizures. It has been found that the above phenomenon provides a simple quantitative technic for the laboratory assay of potentially useful anti-convulsant drugs. The details of these experiments have been reported elsewhere.[32,34,35]

Table II summarizes the ability of Tridione, phenobarbital and diphenylhydantoin to elevate the experimentally lowered electroshock threshold. Tridione and phenobarbital are approximately equally effective, whereas diphenylhydantoin is less so. Again it may be emphasized that although diphenylhydantoin is unable significantly to alter the normal electroshock threshold, it is capable of elevating the experimentally lowered threshold.

TABLE II

EFFECT OF TRIDIONE, PHENOBARBITAL AND DIPHENYLHYDANTOIN ON ELECTROSHOCK THRESHOLD LOWERED BY CELLULAR HYDRATION

Drug	No. of Rats	Dose* Mg./Kg.	Electroshock Threshold† m.a. (Mean ± S.E.)			Per Cent Increase in Hydration Threshold (Mean ±S.E.)
			Normal	4 Hr. after i.p. Glucose		
				Control	Drug	
Tridione	12	400	31±1.4	13±0.6	23±1.5	79±5.1
Phenobarbital	12	45	32±1.0	14±0.9	27±1.3	92±6.1
Diphenylhydantoin	10	50	29±0.9	13±0.5	19±0.9	47±3.8

* Given i.p. except for diphenylhydantoin, s.c.
† 0.2 sec. stimulus duration.

4. *Modification of the Pattern of Maximal Electroshock Convulsions.* It has previously been reported by us[40,42,43] that seizures produced in rats, rabbits and cats by electroshock intensities not far above thresh-

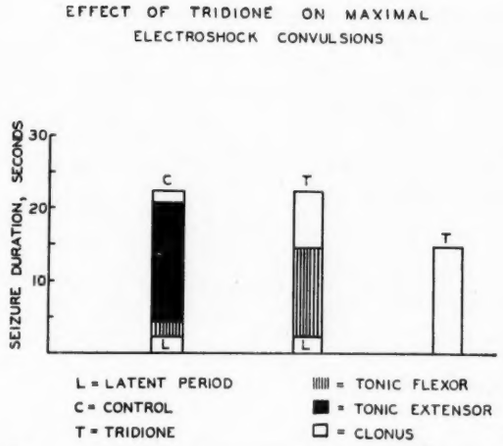

FIG. 1. *Schematic representation of the effect of Tridione on maximal electroshock seizures in rabbits. Current intensity, 300 m.a.; stimulus duration, 0.2 sec. Protective doses (see text) of Tridione abolish the extensor component of the tonic phase (middle column). Larger doses abolish the entire tonic phase.*

old are relatively constant in duration and are characterized by a relatively invariable motor pattern. In brief, the seizure pattern consists of an initial short tonic flexor component, a prolonged tonic extensor component, and a short terminal clonic phase, sometimes absent. Evidence has been adduced to indicate that the above described seizure pattern represents maximal interneuronal facilitation. The physiological properties of such maximal seizures and their modification by drugs have been described.[17,33,43]

A number of anti-convulsant drugs are capable of altering the pattern of maximal seizures in experimental animals. A convenient end point for the comparison of anti-convulsant potencies has proved to be the abolition of the hindlimb tonic extensor component. By dividing the *minimal toxic dose* (that required to produce minimal signs of central impairment) by the *protective dose* (that required to abolish the hindlimb tonic extensor component), a *protective index* is obtained which makes possible a comparison of various drugs. To date, the drug ranking highest by this index is N-methyl-5,5-phenylethylhydantoin-

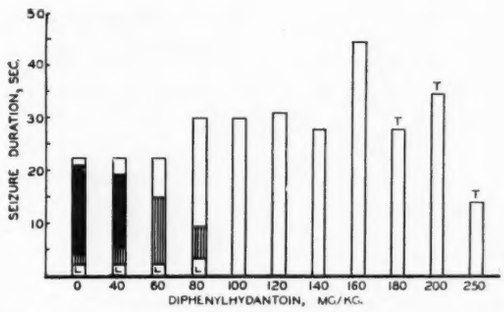

FIG. 2. *The effect of diphenylhydantoin dosage on the pattern of maximal electroshock seizures in rabbits. Current intensity, 300 m.a.; stimulus duration, 0.2 sec. L = latent period. T = toxic dose. The barred, solid black and clear segments of the vertical columns represent tonic flexor component, tonic extensor component and clonic phase of the maximal convulsion, respectively. Observe the effect of increasing doses on seizure duration and pattern.*

ate.*[,33] Of the better known clinically employed agents, diphenylhydantoin, phenobarbital and Tridione rank in the order named.[43] Bromide is less effective and glutamic acid is completely without activity. It has been shown by us that glutamic acid exhibits no anti-convulsant potency by any laboratory procedure yet devised.[17]

TABLE III

RELATIVE ABILITY OF ANTI-CONVULSANT DRUGS TO MODIFY MAXIMAL ELECTROSHOCK SEIZURES IN RABBITS*

No. of Rabbits	Agent	Protective Dose Mg./Kg. (P)	Toxic Dose Mg./Kg. (T)	Protective Index (I = T/P)
10	Tridione	500	875	1.7
27	Phenobarbital	15	35	2.3
47	Diphenylhydantoin	60	180	3.0

* 300 m.a., 0.2 sec. (5 times threshold current).
P = dose required to abolish tonic extensor component of seizure in 50% of rabbits.
T = dose required to produce minimal signs of central impairment (ataxia, deficit in contact placing reaction, drowsiness, etc.).

Figures 1 and 2 illustrate the modification of the maximal seizure pattern by Tridione and diphenylhydantoin, respectively. The

* Kindly supplied by S. M. Fossel of the Sandoz Chemical Works, Inc.

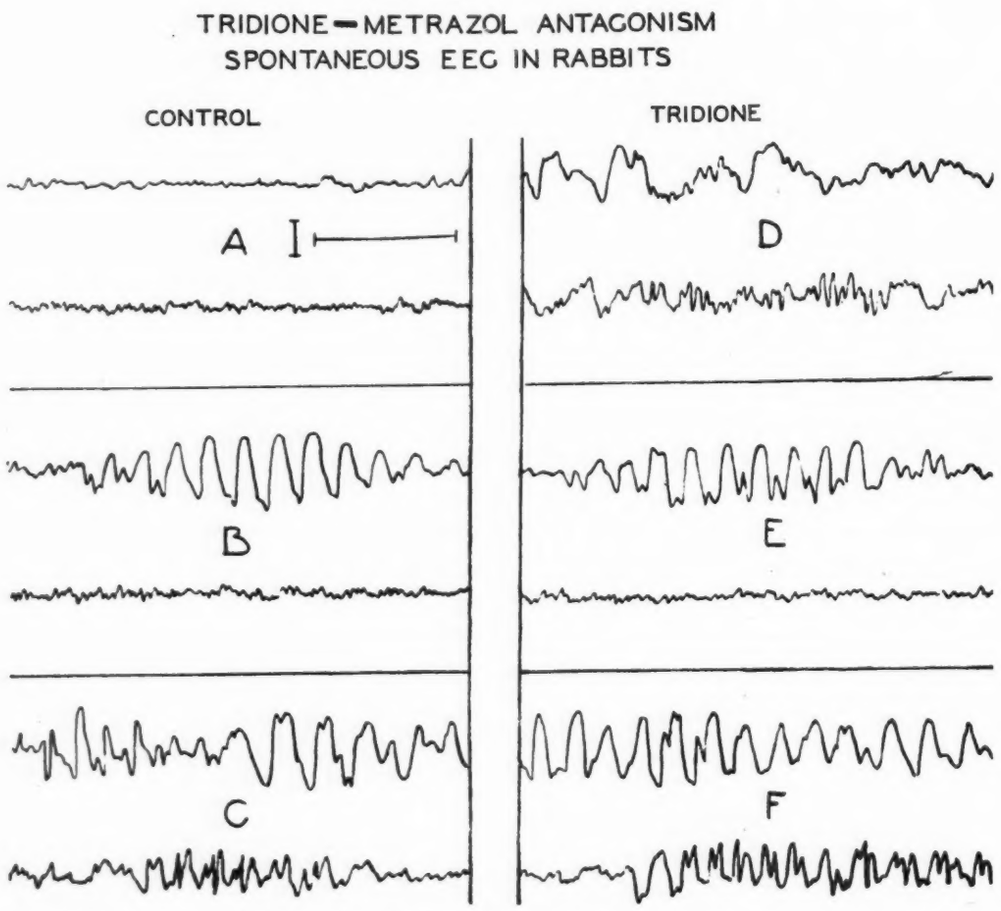

FIG. 3. *Spontaneous EEG of the rabbit: Tridione-metrazol antagonism.* A, B *and* C, *control.* D, E *and* F, *after Tridione i.p.*, 700 *mg./kg. Time and amplitude* (*as shown in* A)*: horizontal line indicates one second; vertical line*, 100 *microvolts. EEG recorded from epidural electrodes, transoccipital* (*upper tracing in each pair*) *and transfrontal* (*lower*).

A, *control EEG without medication. Low voltage fast activity.* B, *episodic slow dysrhythmia in occipital lead after metrazol*, 10 *mg./kg. by slow i.v. infusion.* C, *almost continuous diffuse dysrhythmia after metrazol*, 80 *mg./kg., prior to overt seizure.* D, *irregular delta activity with spindles in motor lead* ("*sleep*" *EEG*) *after Tridione.* E, *occasional slow-wave episode after metrazol*, 85 *mg./kg. EEG otherwise normal.* F, *almost continuous diffuse dysrhythmia after metrazol*, 110 *mg./kg. This series illustrates the specificity of the Tridione-metrazol antagonism and the degree of protection afforded by Tridione against subconvulsive metrazol dysrhythmia.*

comparative potencies of Tridione, diphenylhydantoin and phenobarbital in rabbits are given in Table III. Similar data have been obtained for rats and cats[43] and for man.[39]

5. *Modification of Non-convulsive EEG Discharges Induced by Cortical Stimulation.* Various EEG effects of phenobarbital and other barbiturates have been described. [1,4,6,9] and others. We have found that Tridione and phenobarbital do not significantly affect the EEG in monkeys, rabbits and cats when given in doses less than those producing minimal signs of neurological depression. In larger doses, the typical EEG alteration is characterized by bursts of fast waves with intervening irregular slow wave activity typical of normal sleep. In contrast, diphenylhydantoin failed to cause EEG signs of sedation, even in toxic doses. The effect of Tridione on the human EEG is described later.

A more accurate analysis of cortical electrical activity has been made possible by recording the secondary cortical discharges following contralateral cortical stimulation with single condenser shocks. These discharges are closely related to the spontaneous electrical activity of the cortex at all stages of excitation and depression, but have the advantage of greater reproducibility.[37,41] When doses were employed which produce neurological depression, the effect of Tridione and phenobarbital on the discharge pattern was essentially that described above for spontaneous EEG activity, namely, the production of a "sleep record." Smaller doses were without influence on the pattern of the evoked discharges. However, Tridione and phenobarbital in non-toxic doses moderately elevated the threshold for such evoked cortical discharges. In contrast, diphenylhydantoin even in toxic doses neither elevated threshold nor modified discharge pattern. Tridione and phenobarbital also prevented the typical modification in cortical discharge pattern produced by subconvulsant doses of metrazol. Tridione was twice as effective as phenobarbital in this respect, whereas diphenylhydantoin was inactive. The results are illustrated in Figure 3.

6. *Prevention of Metrazol-induced Petit Mal-like Cerebral Dysrhythmias.* Subconvulsant doses of metrazol given to rabbits subcutaneously or by slow intravenous infusion have been found by us to evoke spontaneous brief episodes of high amplitude, regular slow wave activity, with occasional alternating spike components but not accompanied by an overt seizure.[38] These discharges resemble in many respects the subclinical dysrhythmic episodes found in patients with petit mal. The dose of metrazol required for production of such discharges was found to be increased by Tridione (Fig. 4) and phenobarbital, but not by diphenylhydantoin. In equivalent non-depressant doses, Tridione was approximately twice as effective as phenobarbital. Spike-dome dysrhythmia produced by fluoroacetate in dogs is also specifically prevented by Tridione.[2,3]

II. CLINICAL STUDIES

Therapy of Convulsive Disorders. Eleven patients with slow wave EEG discharges and clinical seizures resembling petit mal were selected for Tridione therapy and study. The age and sex distribution of the patients, the various EEG types and the clinical results obtained with Tridione are shown in Table IV.

In all four patients with history of petit mal only and with a pure petit mal EEG (J. W., E. H., J. H., I. C.), complete clinical remissions were obtained. In two additional patients with petit mal EEG but with histories of both grand mal and petit mal (L. K., D. L.), both types of seizures disappeared under Tridione therapy. Complete remission was also obtained in one patient (W. S.) with atypical petit mal seizures accompanied by a clonic type of EEG discharge.

In the remaining four patients, all of whom had psychomotor as well as other EEG dysrhythmias, Tridione alone was inadequate to control seizures, although petit mal attacks were abolished in two (P. M., A. T.). At the present time one patient (R. C.) shows a substantially greater reduction in petit mal attacks under treatment with phenobarbital and diphenylhydantoin than with Tridione. Two individuals (A. T., A. A.) are completely controlled on Tridione and diphenylhydantoin. The remaining patient (P. M.) shows substantial improvement on Tridione and phenobarbital.

During complete clinical remission as a result of Tridione, the EEG was re-examined in four patients who originally had a pure petit mal type of dysrhythmia. Not

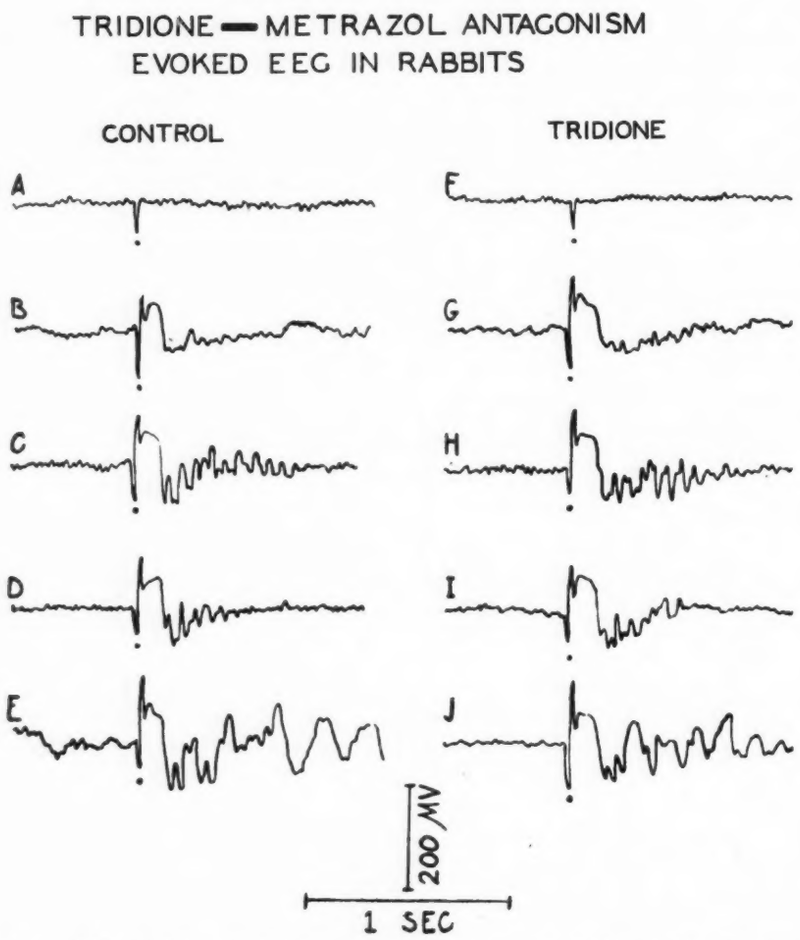

FIG. 4. *EEG dischargee evoked by cortical stimulation in the rabbit: Tridione-metrazol antagonism. Dots indicate polarization artifact following condenser shocks* (50 *microseconds*) *applied to left hemisphere through epidural electrodes. EEG recorded from opposite hemisphere. Upward deflection indicates motor area electronegative to indifferent electrode. Time and amplitude as shown.*

A–E, *control.* F–J, *after Tridione i.p.,* 400 *mg./kg.* A *and* F, *shock polarization artifact only* (10 *volts*). B *and* G, *surface-negative component of evoked discharge. Threshold* 20 *volts in control* (B), 25 *volts after Tridione* (G). C *and* H, *same as above plus long repetitive component elicited by increased voltage. "Light sleep" type of record, rare in control but predominant after Tridione. Threshold* 30 *volts in control* (C), 40 *volts after Tridione* (H). D *and* I, *briefer repetitive component characteristic of waking state, normally present in control* (D); *present after Tridione when* 80 *mg./kg. of metrazol had been administered subcutaneously* (I). *Threshold in both* D *and* I, 30 *volts.* E *and* J, *prolonged slow repetitive "metrazol" discharge following* 40 *mg./kg. of metrazol in control* (E) *and* 130 *mg./kg. of metrazol after Tridione* (J). *Threshold in both* E *and* J, 15 *volts. This series illustrates the quantitatively greater ability of Tridione to protect against metrazol than to elevate electrical thresholds.*

only was the spontaneous EEG found to be normal, but it was now impossible to produce a petit mal discharge by means of the standard hyperventilation test. (Fig. 5.) Tridione failed to abolish the psychomotor type of dysrhythmia in three patients in whom it was possible to re-examine the EEG, despite the complete or nearly complete clinical remission of all seizure types in two of these individuals. In patient A. A., the "petit mal variant" dysrhythmia (classified in Table IV as grand mal) was unaltered.

TABLE IV

TRIDIONE THERAPY OF PETIT MAL

Patient, Age and Sex	Control Period					Tridione Therapy						
	EEG Type	Drug	Seizures per Week			Seizures per Week			Other Drug Added	EEG Type	Toxicity	Tridione Gm./Day
			PM	PS	GM	PM	PS	GM				
J. W. 9M	PM	P, D	45	0	0	0	0	0	..	N	Phot.	1.2
E. H.† 9F	PM	D	200	0	0	0	0	0	..	N	Sed.	0.6
J. H. 17F	PM	P, D, G	100	0	0	0	0	0	..	N	Phot.	0.9
I. C. 11M	PM	P	50	0	0	0	0	0	..	.....	None	0.9
D. L.† 15M	PM	P, D	175	0	2	0	0	0	..	N	Phot.	1.2
L. K. 3M	PM	P, D	100	0	4	0	0	0	..	.....	None	0.3
W. S. 13M	PS, GM	None	‡175	0	0	0	0	0	..	PS	Phot.	1.8
P. M. 17F	PM, PS	P, D	175	0	R	0	25	2	..	.....	Rash	1.8
						4	0	0	P	.....	.....	1.2
A. T. 26F	PM, PS	P, D	100	0	1	0	0	3	..	PM, PS	None	1.5
						0	0	0	D	.....	.....	1.2
R. C. 18M	PM, PS	P, D	30	0	0	15	0	0	..	.....	Phot.	2.1
						3	0	0	*D, P	.....	.....	...
A. A.† 27F	PS, GM	D	10	0	1	15	0	30	..	PS, GM	None	1.2
						0	0	0	D	.....	.....	0.6

P = Phenobarbital
D = Diphenylhydantoin
G = Glutamic acid
* = No Tridione
R = Rare
N = Normal
† Case histories given in the text
‡ = Tonic head component
PM = Petit mal
PS = Psychomotor
GM = Grand mal
Phot. = Photophobia
Sed. = Sedation

Tridione was withdrawn in four patients (J. W., E. H., D. L., W. S.) after complete clinical remission for at least two months. Seizures returned within one to sixteen days. Tridione therapy was resumed when the seizure rate reached fifteen per week, representing a period of one to five weeks without medication, and clinical remissions were again induced. Although we have not as yet observed the reported prolonged freedom from seizures following Tridione withdrawal,[22,24] possibly because our patients had not been in clinical remission for a sufficiently long period of time, we have confirmed the observation that Tridione medication may be stopped abruptly without danger of a sudden return of frequent seizures or of "status epilepticus," differing in this important respect especially from phenobarbital.

In at least five patients the attack rate was sharply increased the first day of Tridione therapy. (Figs. 6, 7, and 8.) In one patient (E. H.) who remained under close clinical and EEG observation during the hours immediately before and after initial Tridione administration, it is thought that the drug itself caused the temporary exacerbation of seizures, but the mechanism is not obvious. In two of the remaining four patients it is possible that the withdrawal of phenobarbital when Tridione therapy was started may have been a major cause of the increased seizure rate. It is also possible that the temporary exacerbation is more apparent than real. Inasmuch as both patients and parents, with understandable anxiety, are much more observant when any new therapy is instituted, mild seizures may have been recorded which ordinarily were overlooked during the control period. Perhaps the emotional stress of being

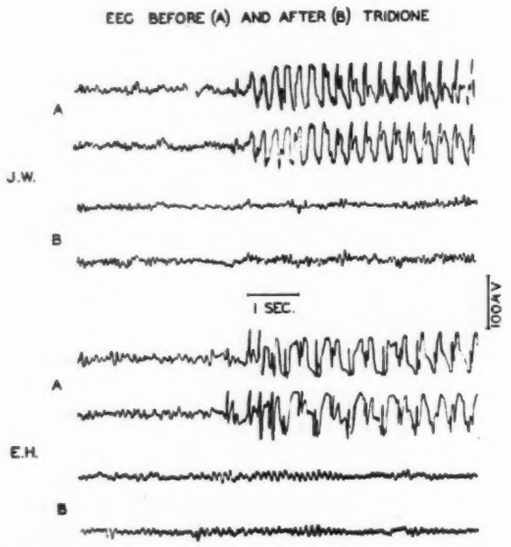

FIG. 5. *Petit mal EEGs of two patients (J. W., E. H.) with histories of pykno-epilepsy. Time and amplitude as indicated.* A-*before, and* B-*after Tridione medication. Electrode placement: In each pair of tracings, the upper and lower leads are left occipital to parietal and right occipital to parietal, respectively. Before Tridione, both patients exhibited typical* 3 *per sec. spike-dome dysrhythmia early in the course of the standard hyperventilation test. During clinical remission there was a complete absence of petit mal dysrhythmia in both patients even after a double hyperventilation test.*

under close observation was also a factor in the transient exacerbation of seizures.

Doses of Tridione varied from 0.3 Gm. per day to 2.1 Gm. per day. In general, age

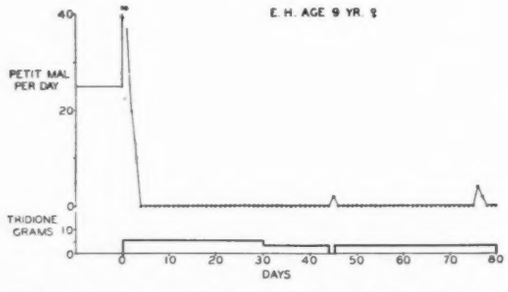

FIG. 6. *Seizure rate before and after Tridione therapy in patient E. H. with a history of pykno-epilepsy and pure petit mal EEG. Details of the case are presented in the text and the EEG is shown in Figure* 5. *Note the increase in seizures during the first day of medication and the rapidity with which clinical remission ensued. A few mild seizures occurred during temporary omission of drug on the forty-fifth day and during an upper respiratory infection on the seventy-sixth day.*

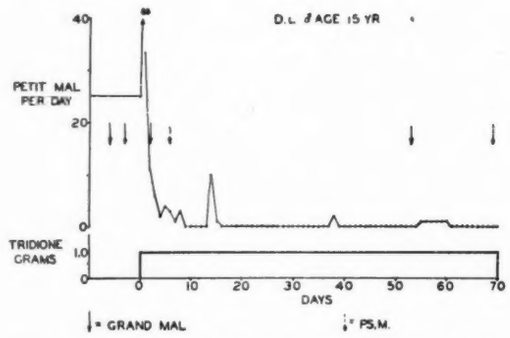

FIG. 7. *Seizure rate before and after Tridione therapy in patient D. L. with a history of pykno-epilepsy associated with occasional grand mal attacks. Case details are presented in the text. Note the increase in petit mal seizures during first day of medication and adequate control of both types of seizures by Tridione alone. The exacerbation on the fourteenth day may have been due to paregoric; that on the thirty-eighth, to alcohol. The psychomotor attack on the sixty-ninth day was questionable.*

and weight determined the initial dosage schedules but adjustments were frequently necessary on the basis of clinical response. In no instance were seizures brought under complete control in less than three days. Once the attacks had ceased entirely for several weeks, it was found possible in several cases to maintain complete remission on doses lower than those necessary for initial medication. (Figs. 6 and 8.) Oc-

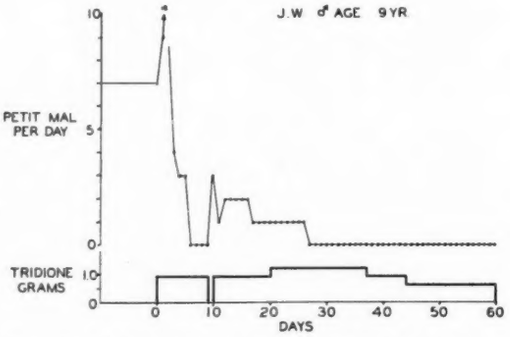

FIG. 8. *Seizure before and after Tridione therapy in patient J. W. with a history of pykno-epilepsy for five years and with a pure petit mal EEG (see Figure* 5*). Note the increase in seizures during the first two days of Tridione medication, the inadequate control of attacks by insufficient dosage, the ultimate clinical remission and the final reduction in dosage without interruption of the remission.*

casional escape from Tridione control of seizures was usually accountable for by intercurrent illness, unprescribed omission of the drug, etc.

Toxic side-effects from Tridione similar to those observed by others[5, 22, 24, 27] were frequent but not sufficiently troublesome to require interruption of treatment. Only four of the eleven patients reported complete freedom from side-actions. Five complained of photophobia and glare especially in bright light. Colored glasses frequently had to be worn. At the height of their photophobia, two patients noted transient inability to see objects distinctly. By adjustment of dosage, it was usually possible to decrease the visual disturbance without return of seizures. Sedation necessitated reduction in dosage in only two patients, but transient drowsiness was experienced by others, particularly early in the course of treatment. Should Tridione prove effective in petit mal only in doses producing sedation, the concomitant use of central stimulants (amphetamine, desoxyephedrine, etc.) may overcome the drowsiness without decreasing the anticonvulsant action.[27] The combined use of phenobarbital and amphetamine in grand mal lends precedent for this suggestion. A transient mild morbilliform rash with slight fever occurred in one patient, but disappeared promptly upon withholding Tridione and did not recur when the drug was cautiously resumed. One patient* not reported in this series experienced severe dermatitis, fever, headache, diarrhea, nausea and vomiting shortly after the initiation of Tridione therapy. The drug was immediately stopped and symptoms cleared, but reappeared upon resumption of Tridione. The petit mal was not improved and further therapy was not attempted.

The following brief case reports are illustrative of the use of Tridione in petit mal and in patients with mixed seizure types:

CASE REPORTS

CASE E. H. A nine-year old girl had pyknoepilepsy for one and one-half years unassociated with other seizure types. There was no relevant family history or record of illness or injury. Physical and laboratory examinations were entirely negative. Diphenylhydantoin therapy was ineffectual.

Seizure rate was 200 per week over a three months' control period of observation.

On three separate occasions, EEG examination showed diffuse symmetrical paroxysmal petit mal dysrhythmia occurring spontaneously and after brief hyperventilation. (Fig. 5.) EEG's of the father and three sisters were normal.

Tridione therapy was started at the dose level of 0.6 Gm. per day. An initial increase in number of attacks occurred during the first twenty-four hours but the seizure rate was reduced to zero by the fourth day of treatment. (Fig. 6.) In this patient it is believed that the temporary exacerbation of seizures was due to the drug itself. Complete clinical remission continued uninterrupted except for brief intervals (upper respiratory infection, temporary omission of medication, etc.). The EEG was re-examined during clinical remission and found to be normal (Fig. 5), even vigorous hyperventilation (two periods of hyperventilation lasting two minutes each with a minute of rest intervening) failing to elicit dysrhythmia. No side-effects were noted except mild sedation which disappeared upon adjustment of dosage. After absence of seizures for two months, Tridione was temporarily withheld. The EEG remained normal during the first week and freedom from clinical seizures persisted for ten days. Occasional mild attacks then occurred. Tridione was again administered three weeks after withdrawal and complete clinical remission quickly ensued.

CASE D. L. A fifteen-year old boy had pyknoepilepsy for four years with associated grand mal for seven months. The average petit mal attack rate was 175 per week; grand mal, two per week. Family history was negative except for migraine. Rapid skeletal growth and occipital

* We are indebted to Dr. S. S. Kauvar of Denver, Colorado for the clinical data on this patient.

headaches were associated with the onset of grand mal but physical and laboratory examination were entirely negative. Phenobarbital and diphenylhydantoin, alone and combined, gave no relief from petit mal but may have reduced somewhat the grand mal attack rate.

EEG examination revealed diffuse symmetrical paroxysmal petit mal dysrhythmia occurring spontaneously and after brief hyperventilation. EEG's of the mother and sister were normal.

Tridione therapy was started at the dose level of 1.2 Gm. per day. An increase in seizure rate (from 25 to 85 per day) occurred during the first twenty-four hours, but the petit mal seizure rate was reduced to zero by the ninth day. (Fig. 7.) Complete clinical remission of petit mal continued without interruption except for three brief intervals, two of which were known to coincide with unprescribed ingestion of drugs (paregoric, alcohol). Grand mal was also considerably benefited by Tridione alone, the seizure rate being reduced from two per week to only one attack in a period of over six months. One questionable psychomotor seizure also occurred.

The EEG was re-examined during clinical remission and found to be normal, even after vigorous hyperventilation. No toxic side-effects were observed other than moderate photophobia, controlled when troublesome by wearing colored glasses.

After three months of Tridione therapy, the drug was withdrawn. Freedom from clinical seizures continued for sixteen days at which time occasional mild petit mal but not grand mal recurred. Tridione was again administered five weeks after withdrawal, and complete clinical remission was restored in one week.

CASE A. A. A twenty-seven-year old female had a long history of seizures dating back to the age of three when attacks diagnosed as petit mal were first observed. Falling seizures without convulsions started at the age of six. Grand mal appeared at the age of thirteen and a particularly severe and prolonged grand mal episode at this time was followed by left-sided hemiplegia which cleared slowly over a period of five months. The patient was periodically studied at several neurological clinics. Complete roentgenographic examinations including pneumo-encephalograms were negative. EEG examination elsewhere disclosed focal right parietal dysrhythmia of an unstated type in addition to a diffuse dysrhythmia, also undescribed. Physical examination was negative except for some residual weakness and slight atrophy of the left extremities. A variety of medications had been employed. When first seen by us the patient was on diphenylhydantoin and a modified ketogenic diet. Seizures clinically resembling petit mal were occurring at the rate of ten per week. Grand mal attacks averaged one per week. The family history was negative.

Diphenylhydantoin was discontinued, and an EEG examination performed four days later revealed diffuse high amplitude slow wave dysrhythmia (5 per sec.) and paroxysmal focal dysrhythmia (2 per sec. spike and slow wave, "petit mal variant") in the right parietal region. Hyperventilation did not modify the EEG and did not elicit a typical petit mal dysrhythmia.

Tridione therapy was started at the dose level of 1.2 Gm. per day, and diphenylhydantoin was not resumed. The grand mal attack rate increased to five per day by the sixth day. The attacks were severe and followed by prolonged confusion and drowsiness. Petit mal was not significantly altered. Diphenylhydantoin was immediately resumed at the former dose level (0.3 Gm. per day) and the Tridione increased to 1.5 Gm. per day. Despite this regimen, drowsiness, disorientation, and agitated depression became so severe that the patient was hospitalized. The possibility of a toxic (drug) psychosis was entertained and Tridione was discontinued. EEG examination at this time was similar to that seen initially. However, slow but complete clearing of the psychosis concomitant with disappearance of grand mal over a period of two weeks and resumption of Tridione without untoward effect made the diagnosis of a toxic psychosis unlikely. It is believed that the acute psychotic episode was directly attributable to the withdrawal of diphenylhydantoin and the resulting marked exacerbation of the grand mal. After several adjustments of dosage schedule, the patient became free of all types of seizures on diphenyl-

hydantoin (0.2 Gm. per day) and Tridione (0.6 Gm. per day). No untoward reactions to Tridione were observed.

The experience in this case indicates the difficulties which may be encountered in a patient with mixed seizure types when medication for grand mal is suddenly replaced by Tridione alone.

COMMENTS

Until the introduction of Tridione there was no adequate therapy for petit mal. Phenobarbital and diphenylhydantoin afforded partial relief in a small number of cases and an occasional patient responded to amphetamine or caffeine. More frequently, medication with bromide, phenobarbital or diphenylhydantoin either afforded no relief or exacerbated the seizures. Other barbiturates and glutamic acid were likewise ineffective. Inasmuch as approximately 45 per cent of the nearly 800,000 epileptics in the United States have petit mal and approximately 8 per cent have petit mal unaccompanied by other forms of seizures,[20] the discovery of Tridione as a specific agent in the symptomatic treatment of the petit mal triad represents an important therapeutic advance.

The results of the laboratory investigations presented above indicate that Tridione has unique pharmacological properties as an anti-convulsant, especially when compared with diphenylhydantoin and phenobarbital. Tridione but not diphenylhydantoin specifically antagonizes the convulsant effects of metrazol, raises the threshold for petit mal-like slow wave EEG dysrhythmias induced by metrazol, elevates the threshold for evoked cortical discharges and raises the normal electroshock seizure threshold. Tridione is inferior to diphenylhydantoin in ability to alter the pattern of maximal electroshock convulsions, and superior to it in ability to elevate electroshock seizure threshold lowered by cellular hydration. Tridione is not significantly different from phenobarbital with regard to indices involving electrical seizure thresholds, but is approximately twice as effective with regard to antagonizing the convulsant and subconvulsant EEG effects of metrazol. It is inferior to phenobarbital in ability to alter the pattern of maximal electroshock convulsions.

Of all the indices examined, the antagonism to metrazol represents the most striking anticonvulsant property of Tridione. Perhaps the specificity of Tridione in the therapy of petit mal may be elucidated by a better understanding of the mechanism involved in the metrazol-Tridione antagonism. To this end, experiments are being conducted which include studies of the electrolyte and enzymatic effects of these two drugs. Finally, on the basis of the animal experiments, it is suggested that metrazol is the best antidotal therapy for Tridione overdosage, the incidence of which may increase with the growing clinical use of Tridione.

In general, the clinical results obtained by us are in agreement with those reported by others. Particularly instructive is the finding that preliminary EEG examination provides a sounder basis than the clinical history of seizure type for deciding whether Tridione should be used, either alone or in combination with other drugs.

The exacerbation of petit mal seizures observed during the first twenty-four hours of Tridione therapy has not been reported previously to our knowledge. Possible explanations for this phenomenon have been presented.

A remarkable feature of Tridione therapy of petit mal, observed by others[22,24] and confirmed by us, is the fact that once complete clinical remission has been obtained, it is impossible to evoke a petit mal EEG discharge even by strenuous hyperventilation. (Fig. 5.) Freedom from petit mal

attacks may persist for days or weeks after cessation of Tridione medication,[22,24] that is, for a period of time considerably beyond the chemical persistence of the drug in the body.[27] It is of interest to note that the salutary effect on the petit mal EEG has been observed within a few hours after intravenous Tridione administration.[11]

Toxic effects from Tridione include drowsiness, confusion, and tremor; photophobia, disturbances in color vision, and scotomas; dermatitis; and, very rarely, blood dyscrasia.[27] Sedation and photophobia are the most common side-actions and ordinarily do not necessitate cessation of medication. Tridione should be withdrawn promptly upon the occurrence of dermatitis, scotomas, anemia or leucopenia.

In the light of our own clinical experience and that reported in the literature, tentative recommendations for therapy of petit mal may be made, as follows:

1. If a patient has a clinical history of petit mal only and also a pure petit mal EEG, Tridione alone constitutes the best possible therapy. Complete cessation of seizures may be anticipated. Transient exacerbation of seizures by Tridione during the first twenty-four hours is not a contraindication to its use.

2. If a patient has a clinical history of petit mal and petit mal EEG but also has occasional grand mal for which therapy is not being administered, Tridione alone may be adequate to control both the petit mal and grand mal.

3. If a patient has both a petit mal history and petit mal EEG and also has grand mal which is under therapeutic control, Tridione medication should be added for the purpose of controlling the petit mal. Grand mal medication, particularly phenobarbital, should not be withdrawn when Tridione is started. If such withdrawal is contemplated, it should not be attempted until the petit mal has been under control for several months. Either diphenylhydantoin or phenobarbital may be prescribed for grand mal in conjunction with Tridione for petit mal, the evidence to date being insufficient to warrant a preference.

4. If a patient has both a petit mal history and petit mal EEG but in addition has a psychomotor EEG (high amplitude regular 4 to 6 per sec. discharge) and is not under medication, Tridione alone may decrease the seizure rate, but the result may not be as good as that obtained with a combination of Tridione and diphenylhydantoin. Cases reported in the literature[5,24] would indicate that if a patient has both psychomotor seizures and a psychomotor EEG and is not adequately controlled by diphenylhydantoin, the addition of Tridione may bring about more satisfactory clinical remission. If the patient is not on therapy, Tridione may be employed alone, but diphenylhydantoin may have to be added subsequently. It has been our experience that clinical improvement may not be paralleled by improvement in the psychomotor EEG.

5. If a patient has a "petit mal variant" type of EEG, phenobarbital or diphenylhydantoin is probably superior to Tridione. Tridione may be added if there is clinical evidence of petit mal seizures.

6. Tridione is a new drug. Clinical experience with it is as yet limited. It is capable of causing toxic effects, some of which are serious. Therefore, Tridione should be employed only in cases exhibiting clear indications for its use. Patients receiving Tridione should be under close medical surveillance.

SUMMARY AND CONCLUSIONS

1. The anti-convulsant properties of Tridione have been compared in animals with those of diphenylhydantoin and phenobarbital by six different laboratory technics. Of all the results obtained, the marked

antagonism to metrazol is the property which most sharply distinguishes Tridione from both diphenylhydantoin and phenobarbital. Of particular significance in relation to the known specificity of Tridione against petit mal is its ability to abolish the petit mal-like EEG dysrhythmia produced in animals by metrazol.

2. On the basis of EEG and clinical study of a selected group of patients with slow wave dysrhythmias, specific recommendations have been advanced for the clinical use of Tridione alone or in combination with other drugs.

3. A sharp rise in seizure rate may be observed in petit mal patients during the first twenty-four hours of Tridione therapy. This transient exacerbation is not a contraindication to the drug, and may be followed by complete clinical remission.

4. It has been confirmed that even vigorous hyperventilation fails to evoke petit mal EEG dysrhythmias once complete freedom from seizures has been obtained. Restoration of the EEG to normal is added evidence for the specificity of Tridione in petit mal.

5. Although freedom from seizures may continue for days or weeks after discontinuation of Tridione, it is suggested that withdrawal should not be attempted until the patient has been seizure-free for many months. However, abrupt cessation of Tridione medication does not entail the danger of "status epilepticus."

6. Drug treatment for associated grand mal should not be stopped when Tridione therapy for petit mal is initiated.

7. If psychomotor EEG dysrhythmia is associated with a petit mal history, diphenylhydantoin combined with Tridione is probably the treatment of choice. An occasional patient may respond well to Tridione alone, even though the psychomotor EEG is not significantly altered.

8. Toxic side-effects to Tridione include sedation, visual sensitivity to bright light and occasionally dermatitis. As a rule, untoward reactions are not troublesome to the point of necessitating cessation of medication. Yet the occurrence of photophobia is a definite disadvantage, and the search for effective drugs lacking this property should continue.

9. Preliminary EEG examination provides a sounder basis than clinical history of seizure type for deciding whether Tridione should be used, alone or in combination with other agents.

10. Tridione is a new drug and consequently several years may be required for a final estimate of its clinical status. Nevertheless, it is unexcelled to date as a specific symptomatic therapy for petit mal. Elucidation of its mechanism of action should provide insight into the pathological physiology of convulsive disorders of the petit mal type.

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Effects of Total Pancreatectomy in a Patient with Diabetes*

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We wish to report physiologic and metabolic observations on a completely pancreatectomized man.* The patient, already diabetic enough to require considerable amounts of insulin, had a carcinoma of the pancreas and underwent resection of that organ, together with the entire duodenum, spleen and left adrenal, all but a fragment of the stomach and most of the omentum. He recovered sufficiently to be up and about his room, but died some fourteen weeks after operation with recurrence of the neoplasm. Autopsy failed to reveal any residual pancreatic tissue.

CASE REPORT

F. W., No. 328218, an unemployed white male, aged fifty-two, was first admitted to the Albert Merritt Billings Hospital February 24, 1944, with the chief complaint of diarrhea of two years' duration. The diagnosis of sprue had been made, but treatment directed against this disease had been relatively ineffective. Nine months before admission, with the onset of polyuria, thirst and voracious appetite, the blood sugar had been found to be elevated and the diagnosis of diabetes had been made, but the patient had refused to take insulin. He had lost approximately fifty pounds in the preceding two years. His father had had diabetes and his mother and maternal grandfather had died of carcinoma.

On physical examination, the patient was emaciated: height 188.6 cm. (74 in.), weight 55.5 kg. (122 lb.). Temperature, pulse and respiration were normal. The skin and mucous membranes were dry. The tongue was coated, but showed no atrophy. The thyroid was palpable but not definitely enlarged. The heart and lungs appeared normal. The blood pressure was 114/70. A sharp liver edge was barely palpable. The spleen was not enlarged. No abdominal masses were felt, and rectal examination revealed nothing abnormal.

Laboratory findings were reported as follows: Hemoglobin 13 Gm. per 100 ml.; red blood cells 4,380,000 per cu. mm.; white blood cells 9,000; differential count normal. The urine contained 4 plus sugar and a trace of acetone but was otherwise normal. The fasting blood sugar was 363, cholesterol 147, total lipids 800, calcium 9.6 mg. per 100 ml.; carbon dioxide 30.5, chlorides 93.4 and sodium 133 mM. per liter. The plasma proteins were 6.05 Gm. per 100 ml. (albumin 3.69, globulin 2.36). The value for serum amylase was 68 units. The stools were liquid to mushy, had a cheesy odor, were acid to litmus and contained an excess of fat and undigested food particles. Cultures revealed Micrococcus psilosis but no other pathogens, and no ova or vegetative forms of Entameba histolytica were found. A histamine test of gastric secretion showed a maximum of 60 clinical units at fifty minutes. *X*-rays of the esophagus, stomach and

* This case has been reported in preliminary form elsewhere.[45] The surgical aspects have been described by Brunschwig, Ricketts, and Bigelow.[9]

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duodenal bulb were normal. The basal metabolic rate was − 19 per cent.

Because of the patient's emaciation and voracious appetite, he was given a high-caloric diet which, during March, consisted of C 701, P 102 and F 99. With protamine zinc insulin, 35 units, and crystalline insulin, 10 units per day, the blood sugars varied from 102 fasting to 268 mg. per cent in the afternoon, and the twenty-four-hour excretion of glucose ranged from 8 to 15 Gm. Diarrhea continued and the feces contained an excess of fat and nitrogen. During the latter part of March, the patient developed marked pitting edema of the feet and ankles, for which no cause could be found except an increased capillary fragility as demonstrated by the tourniquet test.* For three weeks during April, the patient consumed a diet of C 900, P 225, F 100 (5,400 calories), requiring 60 units of protamine zinc and 40 units of crystalline insulin daily. He was still hungry. From May 3rd to 12th, the diet was C 398, P 200, F 12 (glucose equivalent 500 Gm.), the total insulin dose varied from 40 to 65 units per day and the blood sugars ranged from 87 fasting to 273 mg. per cent in the afternoon, with the excretion of 6 Gm. or less of sugar per twenty-four hours. There were occasional insulin reactions. Abdominal pain, chiefly hypogastric but sometimes epigastric, occurred from time to time and was occasionally severe. The diagnosis was thought to be chronic pancreatitis, producing diabetes and diarrhea. Carcinoma of the pancreas was considered, but was deemed unlikely in view of the two-year history and the remarkable gain in weight during treatment. The patient was discharged May 14th weighing 72.4 kg. (159 lb.), which represented a gain of 16.7 kg. (36.7 lb.) in eleven weeks.

During the summer, the patient was followed in the clinic. In July, he complained of severe pain in the right upper quadrant, lasting for three days with an exacerbation of diarrhea. In August he developed jaundice, clay-colored stools, dark urine and pruritus.

He was readmitted to the hospital August 29th. The weight was 68.2 kg. (150 lb.). Physical examination revealed no new findings except the jaundice and a more easily palpable liver. There were no abdominal masses. On a diet of C 400, P 200, F 35, and with from 55 to 80 units of insulin per day, glycosuria was satisfactorily controlled. Laparotomy performed September 7th (A. B.) revealed a carcinoma of the pancreas with extensive infiltration of the neighboring organs and tissues. Total extirpation of the pancreas, duodenum, spleen and left adrenal, together with all but a fragment of the stomach and a large portion of the omentum, was performed. Examination of the pathologic specimen showed the midportion of the body and tail of the pancreas to be replaced by carcinoma which, on microscopic study, was found to be of the duct cell type. Many of the islets in the remainder of the pancreas showed changes consistent with ordinary diabetes mellitus (Dr. George Gomori). (Fig. 1.)

The postoperative course was remarkably uneventful, nutrition being maintained by parenteral glucose and Amigen,* and glucosuria being kept within reasonable limits (8 to 32 Gm. per day) with from 30 to 100 units of insulin per day. During this period and thereafter until shortly before death the patient received by parenteral injection 10 mg. of Synkavite† daily, and 2 cc. of Betaline‡ and 2 cc. of Cenolate§ every second day. Feeding by mouth was begun on the ninth day and was well tolerated. On September 22nd, fifteen days after operation, the patient was up in a chair. For three months after this date special studies, which will be described presently, were carried out. The diarrhea was definitely more severe than before operation and the patient lost weight to about 56 kg. (123 lb.) during the first five weeks. The weight was then maintained at this level until two weeks before death. When the diet was kept at C 400, P 100 and F 12 (glucose equivalent

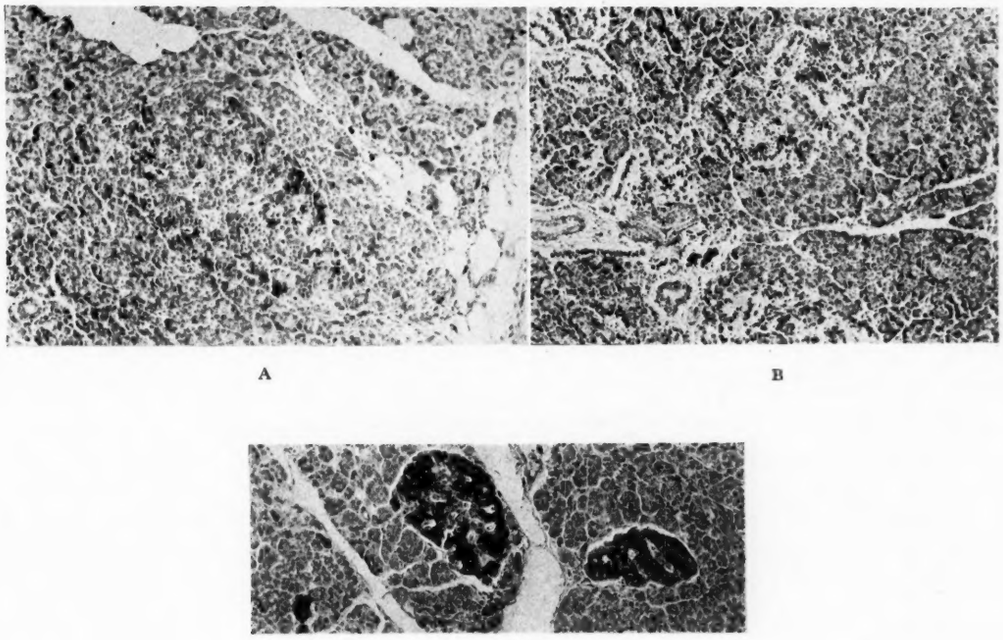
* A similar edema was observed in another patient with well controlled diabetes and pancreatic steatorrhea when he was placed on a very high carbohydrate diet. The phenomenon may be related to a high glycogen content of the skin.

* A 5% solution of a pancreatic hydrolysate of casein with 5 per cent dextrose (Mead Johnson).

† 2-methyl-1, 4 naphthohydroquinone diphosphoric ester tetra sodium salt; high vitamin K activity (Hoffmann-LaRoche).

‡ 2 cc. ampule contains 10 mg. thiamin chloride, 4 mg. riboflavin, 150 mg. nicotinamide, 5 mg. pantothenic acid, 10 mg. pyridoxine hydrochloride (Lilly).

§ 2 cc. ampule contains ascorbic acid, 0.100 Gm. as sodium salt (Abbott).



A B C

FIG. 1. A, *a large island consisting almost exclusively of alpha cells and containing only a small number of beta cells (dark). Magnification* × 115. B, *"ribbon type" islets. Magnification* × 115. C, *normal islets from a non-diabetic patient, showing many beta cells (dark) Magnification* × 115. *Description of the pathology of the islands of Langerhans (Dr. George Gomori): With ordinary stains the overwhelming majority of the islands look entirely normal except for an increase in size. An occasional islet shows hyalinosis. In addition there are a large number of "ribbon type" islets (W. G. MacCallum, Am. J. M. Sc.,* 133: 432, 1907), *many of which show thickened connective tissue stroma. Specific stains (G. Gomori, Am. J. Path.,* 17: 395, 1941) *show an extremely small number of beta cells, most of the islets being composed of over* 90 *per cent alpha cells. The granulation of the remaining beta cells seems to be normal. The alpha cells are large and richly granulated. In the "ribbon type" islets the cells are either agranular and unrecognizable as to type or contain a small number of normal appearing beta cells and very few alpha cells.*

457 Gm.), glycosuria varied from 0 to 36 Gm. in twenty-four hours with a daily insulin dose of from 30 to 60 units, averaging about 40 units. By October 9th, jaundice was no longer visible and the liver was not palpable. On October 10th the Van den Bergh test of the serum showed 1.8 mg. per cent direct and 2.8 indirect of bilirubin with an icteric index of 19; a bromsulphalein test of liver function (dose, 5 mg./kg.) resulted in 36 per cent retention in 20 minutes. On October 24th, the values for the Van den Bergh test were 1.2 direct and 1.7 indirect, the icteric index being 11. On October 31st, with a dose of 2 mg./kg., there was 40 per cent retention of bromsulphalein in five minutes and no retention in thirty minutes. About October 17th, a tumor mass was palpable in the region of the incision. This grew steadily and about November 20th abdominal pain recurred with increasing severity, requiring opiates. The patient developed anorexia and appeared to be going downhill rapidly. On December 4th all insulin was withdrawn for three days. On December 12th insulin was withheld permanently and the patient died December 18th in typical diabetic coma.

Autopsy was performed by Dr. S. D. Wu on December 18th, approximately five and one-half hours after death. An abstract of the pathologic report follows:

. . . The body is that of a markedly emaciated, icteric adult male, weighing 33.2 kg. (73 lb.) and measuring 167 cm. (67 in.) in length. The body is virtually skin over bones . . . The primary incision reveals practically no subcutaneous fat in the anterior abdominal wall. The peritoneal surfaces are thoroughly studded

everywhere with large numbers of grayish white and firm tumor nodules, averaging .5 cm. or so in diameter. These are more especially numerous in the anterior parietal peritoneum, the fascia and muscles to just beneath the skin. They are also numerous on the under surfaces of the diaphragm and in the omentum. Most of the stomach, all of the duodenum and the spleen are missing. . . . The heart weighs 280 Gm. and is normal in shape and size, only it is jaundiced. . . . The aorta and coronary arteries show the usual degree of atherosclerosis. . . . The liver weighs 1,520 Gm. and shows a number of small tumor nodules scattered about in the capsule. The organ is icteric. The gallbladder is normal. The common bile duct is dilated, though not now obviously obstructed. . . . The pancreas as such is completely missing as far as can be judged by gross examination. In the region of the organ is a large and oblong piece of firm fibrous tissue with tumor imbedded in it. Serial sections of this reveal no grossly recognizable pancreas. . . . The remaining small segment of stomach, together with the lower end of the esophagus, is anastomosed to the upper jejunum. . . . In the middle jejunum there is a side to side entero-enterostomy. More distally in the jejunum the wall of the intestine is anastomosed to the much dilated common bile duct. All these anastomoses are healed, but bordered by neoplastic tissue. The duodenum is missing and there is a blind end at the site of the duodenojejunal junction. The intestinal serosa contains many tumor nodules throughout both the small and the large intestines. The right adrenal is normal. The left is not identified. Both kidneys together weigh 390 Gm. and are swollen and icteric.

The pertinent microscopic sections, reviewed by Dr. Eleanor Humphreys, are reported as follows:

Liver: The liver shows a fatty degeneration in the peripheries and even more in the centers of the lobules. The bile canaliculi are distended with bile while the interlobular connective tissue is the site of a pericholangitis. In most lobules this is an acute process with a predominance of polymorphonuclears but in some, lymphocytes and plasma cells are the outstanding type. The lumens of many of the larger bile ducts contain bacteria, both rods and cocci, but at no place in the sections have these extended through the epithelium of the duct. There is an early, beginning cirrhosis with encroachment of the perilobular connective tissue upon the adjacent liver cords with resulting compression and degeneration. Many of the cords contain glycogen-rich hepatic cells. The cirrhous adenocarcinomatous tissue, composed, for the most part, of columnar epithelial cells lining alveolae or cystic spaces, can also be seen encroaching upon the liver (in the sections taken from the region of the hepatic vein).

Colon: Carcinoma cells can be found growing extensively under the muscularis. . . . A few tumor cells can be found growing in the lymph spaces between the circular and longitudinal muscular coats. . . . There is little inflammatory reaction. *Stomach and Jejunum:* The section passes through the site of the gastrojejunal anastomosis, now represented by a thin line of fibrous tissue. The carcinoma is penetrating through the muscularis into the submucosa of the jejunum and of the stomach. Below the muscularis the infiltrating fibroplastic tumor is forming large, irregular, neoplastic vesicles. . . . *Bile Duct and Jejunum:* . . . Neoplastic tissue has invaded the region of the anastomosis and infiltrates the wall of both jejunum and bile duct. . . . *Adrenal:* The orderly pattern of the cortex is disturbed by poorly demarcated nodules. Most of the cortical cells have eosinophilic granular cytoplasm, and the only cells with clear or foamy cytoplasm (suggesting an abundance of lipids) are found in small islands, near the capsule. Other acini of the glomerular zone are large and acidophilic with gland-like central cavitation. *Thyroid:* Fibrous bands subdivide the gland into nodules of varying size. The proportion of small (fetal type) acini is high, but all nodules contain normal colloid rich acini in considerable numbers. The epithelium is everywhere flat or low columnar. *Hypophysis:* The hypophysis has normal form and internal structure, but superficially, seems to have fewer basophilic cells than normal. Actually, the number is probably within the normal range. The chief abnormality is the comparative rarity of cells filled with deeply basophilic granules. In specially stained sections (Azur-carmine) many

lightly stained basophiles are observed. A small proportion, approximately 10 per cent, of the basophiles contain one or more vacuoles.

METHODS

The patient was confined to the metabolic unit of the hospital at all times and was weighed daily. All food and liquids were weighed or measured. As a rule, all stools were collected and weighed daily, and the twenty-four-hour specimens of urine were collected and preserved in a refrigerator for analysis. Samples of capillary blood for sugar determination were taken frequently, in the postoperative period usually four times daily. The technic of collection of specimens during the balance studies followed standard metabolic practice, aliquots of the food being saved and analyzed along with specimens of excretion.

Chemical determinations were made in duplicate according to the methods of the following authors: *in serum*, carbon dioxide content, Van Slyke and Neill,[55] pH, Hastings and Sendroy;[26] chloride, Wilson and Ball,[59] after digestion according to Van Slyke and Neill;[54] sodium, Butler and Tuthill[11] modified by Eichelberger;[17] potassium, Shohl and Bennett[49] modified by Eichelberger;[17] amylase by the saccharogenic method of Somogyi;[50] lipids, Wilson and Hanner[59] as modified by P. B. Donovan and described by Stewart et al.;[31] calcium, Kramer and Tisdall[31] modified by Clark and Collip;[12] phosphorus, Fiske and Subbarrow;[18] *in capillary blood*, glucose, Miller and Van Slyke;[39] *in plasma*, non-protein nitrogen, Koch and McMeekin[29] (protein was found by multiplying the difference between the total and the non-protein nitrogen by 6.25); total fecal fat, Saxon[48] modified by Fowweather.[20] Total nitrogen of food, feces, urine and plasma was determined by the Kjeldahl technic. Sufficient material to contain the appropriate amount of nitrogen was digested in 300 ml. digestion flasks with concentrated sulfuric acid and sodium and copper sulfates. The ammonia formed was distilled into 50 ml. of 4 per cent boric acid solution and titrated with 0.1 N acid to the bromcresol green end point as described by Meeker and Wagner.[38] Food, fecal and urinary calcium and food and fecal phosphorus were determined by applying the methods used for serum to extracts or aliquots of the dried, ashed materials, made by several extractions with hot 10 per cent hydrochloric acid into volumetric flasks. After cooling they were made to volume and filtered through retentive paper. Dilutions were chosen so that 1 to 3 ml. contained 0.1 to 0.3 mg. of calcium. For calcium determinations such amounts were measured into the special centrifuge tubes, 1 ml. of 4 per cent ammonium oxalate was added, the mixture was roughly neutralized with concentrated ammonium hydroxide, and finally adjusted to pH 4.2 to 4.4 in the presence of bromcresol green. The determination was completed as with serum. For phosphorus, an amount of a dilution containing 0.3 to 1 mg. was used in the determination as described for urine.[18] Inorganic phosphorus could be determined in urine by direct application of this technic.

The preparation and ashing of food and feces for analysis was done as described by Knowlton et al.[30]

Respiratory studies were made with a Tissot apparatus (Dr. Irene Sandiford), gases being analyzed by the Haldane technic.

SPECIAL STUDIES

Effect of Diet and Medication on Fecal Volume. Before operation (Table 1) the average daily weight of feces without medication (March 28th to April 3rd and April 11th to 17th) was not significantly different from the weight when Lilly's enteric coated pancreatin tablets in doses of from 32 to 64 Gm. per day were being administered (April 4th to 8th). Reduction of dietary fat from 100 to 13 Gm. per day produced no important change in the amount of feces (March 28th to April 3rd and April 11th to 17th, as compared with April 18th to 25th); nor did any change result from the intramuscular administration of 3.5 ml. of crude liver extract per day. The fecal volume was appreciably reduced, however, in the period May 3rd to 11th when the carbohydrate of the diet was lowered from 901 to 398 Gm. and when tincture of belladonna, 30 drops, and bismuth subcarbonate, 6 Gm., were administered daily.

TABLE I

EFFECT OF DIET AND MEDICATION ON COMPOSITION OF FECES

Date	Diet			Medication	Stools				
					Average Weight		Total Fat		Total N (Gm./day)
	C	P	F		Wet (Gm./day)	Dry (Per Cent of Wet Wt.)	Gm./day	Per Cent of Dry Wt.	
3-22-44 to 3-25, inclusive	701	102	99	None	934	11.2	20.4	19.5	6.45
3-28-44 to 4-3, inclusive	900	225	100	None	1365				
4-4-44 to 4-8, inc.	900	225	100	Pancreatin, enteric coated, 32 to 64 Gm/day	1488				
4-11-44 to 4-17, inclusive	900	225	100	None	1701				
4-18-44 to 4-25, inclusive	901	227	13	None	1350				
4-26-44 to 5-2, inclusive	901 av.	227 av.	13 av.	Crude liver extract, i.m. 3.5 ml./day	1572				
5-3-44 to 5-11, inclusive	398	200	12	Tr. Belladonna, 30 drops/day. Bismuth subcarbonate, 6 Gm/day	683				
9-7-44	Total pancreatectomy, gastrectomy, duodenectomy, splenectomy, left adrenalectomy								
10-20-44 to 10-25, inclusive	400	101	99	Atropine 0.0018 Gm. daily	2001	14	75.9*	26.6*	12.34*
10-26-44 to 10-29, inclusive	400	101	99	Atropine 0.0018. Powdered pancreatin 30 Gm. daily	1358				
10-31-44 to 11-7, inclusive	400	103	20	Atropine 0.0036. Powdered pancreatin 45 Gm. daily	750				
11-8-44	400	103	20	Powdered pancreatin 45 Gm. daily	5580				
11-9-44	419	103	20	Powdered pancreatin 45 Gm. daily	3360				
11-10-44	400	99	17	Atropine 0.0036 Gm. daily	60				
11-11-44 to 11-19, inclusive	400	103	20	Atropine 0.0036 Gm. daily	870				
11-20, 24, 25	257 to 295	59 to 74	12 to 14	Atrop. 0.0036 Gm., Pancreatin 20–40 Gm. daily	672				
11-21, 22, 23	342 to 419	83 to 104	15 to 20	Pancreatin 40–60 Gm. daily	459				

* Two-day collection 10-24-44 to 10-25-44.

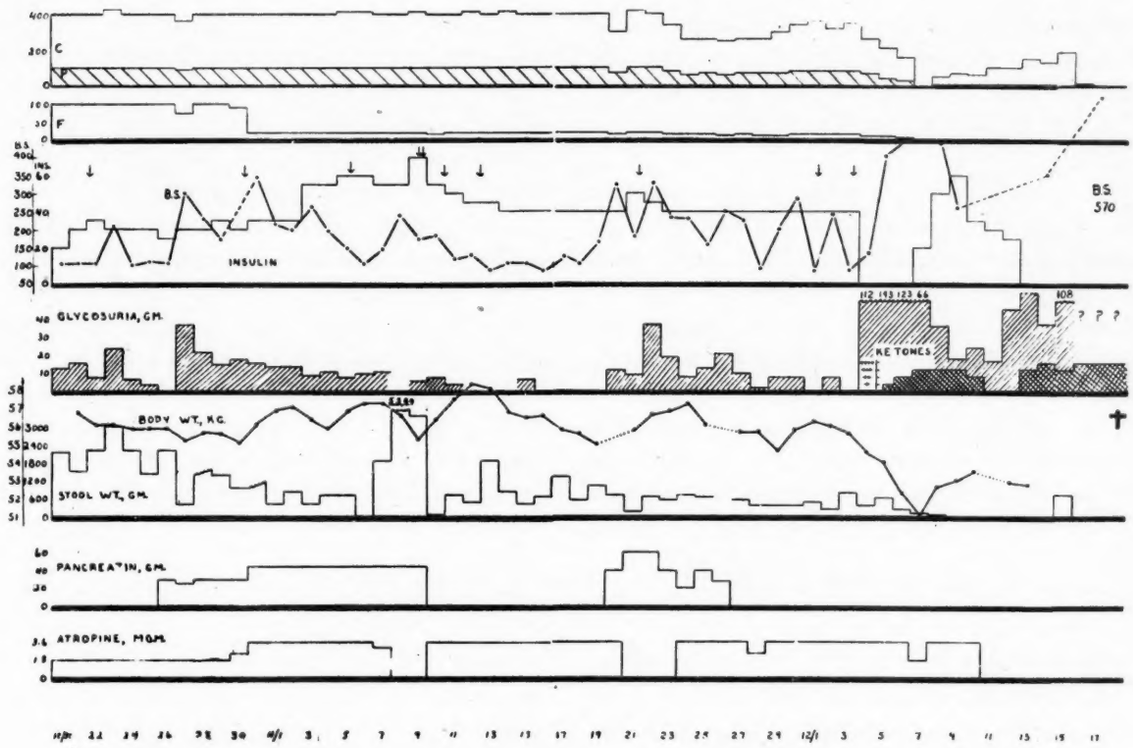


FIG. 2. *Observations from six weeks after pancreatectomy until death; arrows indicate insulin reactions.*

After operation the quantity of feces was so large as to render impractical the collection of specimens for chemical analysis in more than two-day amounts. Fecal weight during the period October 20th to 25th, when the patient was receiving 0.0018 Gm. of atropine sulfate per day, averaged 2,001 Gm. daily. (Table I, Fig. 2.) The addition of 30 Gm. daily of pancreatin in powdered form (Lilly), now feasible because of the absence of gastric juice, was accompanied by a reduction in weight of stools to an average of 1,358 Gm. per day. This was further lowered to 750 Gm. per day when the dietary fat was reduced from 99 to 20 Gm., and when atropine was increased to 0.0036 Gm. and powdered pancreatin to 45 Gm. daily. When atropine was stopped November 8th, despite the continuation of pancreatin, the feces for that day weighed 5,580 Gm.; while in the period November 11th to 19th, with atropine reinstituted and pancreatin withheld, the average daily fecal weight was 870 Gm.

TABLE II
BALANCE STUDIES

Age 53
Weight ..... 56.0 kg.
Height ..... 188 cm.
Total pancreatectomy September 7, 1944
Diet: C 400, P 101, F 99. G = 471. Cal. = 2,895
Last feedings 7:00 P.M. each evening
Crystalline insulin 15-10-5 units
Fasting blood sugar October 24, 101 mg./100 ml.
Fasting blood sugar October 25, 111 mg./100 ml.

Date		Wt. or Vol. (Gm.)	N (Gm.)	Ca (Gm.)	P (Gm.)	Creatinine (Gm.)
10–24	Food	.....	15.98	1.18	1.49	
	Urine	395	2.52	0.12	0.28	
	Feces(4)*	2220(2615)†	12.34 av.	0.98 av.	0.98 av.	0.83
	Balance	.....	+1.12	+0.08	+0.23	
10–25	Food	.....	15.98	1.18	1.49	
	Urine	1075	4.68	0.14	0.59	1.19
	Feces(3)*	1440(2515)†	12.34 av.	0.98 av.	0.98 av.	
	Balance	.....	−1.04	+0.06	−0.08	
Mean	Food	.....	15.98	1.18	1.49	
	Urine	.....	3.60	0.13	0.44	
	Feces	.....	12.34	0.98	0.98	
	Balance	.....	+0.04	+0.07	+0.07	

* Number of stools per day.
† Figures in brackets indicate sum of urine and fecal volumes.

Absorption and Balance Studies. Before operation, no studies of carbohydrate absorption or of reducing substances in the feces were made. Nitrogen balances were not carried out since the urine was not analyzed, but the feces collected March 22nd to 25th contained an average of 6.45 Gm. of nitrogen per day. The patient's ability to absorb fat was not impaired as tested March 16th by following the serum lipids after

a fat meal. During the period March 22nd to 25th, however, with the dietary fat 99 Gm. per day, the patient lost in the stools an average of 20.4 Gm. of fat (19.5 per cent of the dry weight) daily.

After operation, two attempts were made to determine the absorption of carbohydrate by means of the usual tolerance tests. These were unsatisfactory, however, because in each instance the ingestion of the glucose solution was followed within a few minutes by a watery diarrhea. The feces on one occasion gave a 2 plus reduction with Benedict's solution. The blood sugar in one test rose to a maximum of 99 mg. per cent above the fasting level and in another the maximum increase was 81 mg. per cent. During the collection of October 24th to 25th, an average of 37 Gm. of "glucose" per day was found in the feces, as determined by analysis on the filtrate after deproteinization. The significance of this figure is doubtful, however, in view of the possibility that, on the one hand, some carbohydrate may have been destroyed by fermentation and, on the other hand, an indeterminate amount of non-specific reducing substance may have been present. Nitrogen balances, together with those for calcium and phosphorus, are shown in Tables II and III. With a daily intake of 15.98 Gm. nitrogen, the fecal loss averaged 12.34 Gm. (77 per cent of the amount ingested), or at least five times normal. This compares with 6.45 Gm. before operation. Figures for the urinary constituents for October 24th should probably be disregarded because of the possibility of incomplete collection as indicated by the low creatinine value for that day. Assuming the collection of October 25th to be complete, and of this we have no reasonable doubt, it is to be noted that the large loss of nitrogen in the feces was accompanied by the relatively low urinary nitrogen of 4.68 Gm. per day. The patient was thus in a negative nitrogen balance of 1.04 Gm. daily. For the same day the calcium balance was slightly positive and the phosphorus slightly negative. A fat tolerance test was not performed in the postoperative period. Absorption, however, was distinctly poorer than before operation, the feces on October 24th containing 75.9 Gm. of total lipids, or 77 per cent of the fat ingested.

Diabetes. All the observations to be described except where it is otherwise stated, were made after pancreatectomy.

Insulin Requirement: Comparisons of insulin requirement in the pre- and postoperative periods (Fig. 3) were made insofar as possible with conditions constant and in the absence of complicating factors. Before operation, on a diet of C 398, P 200, F 12 (glucose equivalent 511 Gm.), and with the body weight 72 kg., the requirement was from 40 to 65 units per day. From sixteen to twenty days postoperatively, on a diet of C 401, P 102, F 11 (glucose equivalent 459 Gm.) and with the body weight 60 kg., the dose was from 30 to 35 units per day. The apparent reduction in the demand for insulin may have been due first, to the lower glucose value of the postoperative diet, second, to the loss of 12 kg. of body weight and third, to the fact that the amount of insulin in the second observation was actually inadequate, hyperglycemia being present in the latter part of the day. From November 12th to November 19th (Fig. 2), with the patient on the same diet, but with the blood sugar better controlled and diarrhea minimal, the true requirement seemed to be in the neighborhood of 40 units per day.

Sensitivity to Insulin: The patient was relatively sensitive to insulin both before and after the pancreas was removed. Hypoglycemic reactions were common in both periods and their frequency and intensity were seemingly unaffected by the operation.

Diurnal Fluctuations of Blood Sugar: It has been observed by Möllerstrom[40] and others that the blood sugar in human diabetes undergoes spontaneous diurnal fluctuations relatively independent of food intake. These have been attributed to rhythmic variations in the function of the liver,[1,19,27] but it has never been determined whether differences in insulin secretion by the pancreas might contribute to the phenomenon. Our patient, lacking a pancreas, presented an opportunity to test this possibility. While being maintained on 30 units of protamine zinc insulin per day which, as previously demonstrated furnishes a constant supply of insulin from the depots,[37,44] he was fed uniform amounts of carbohydrate every two hours, and for three days the blood sugar was followed at

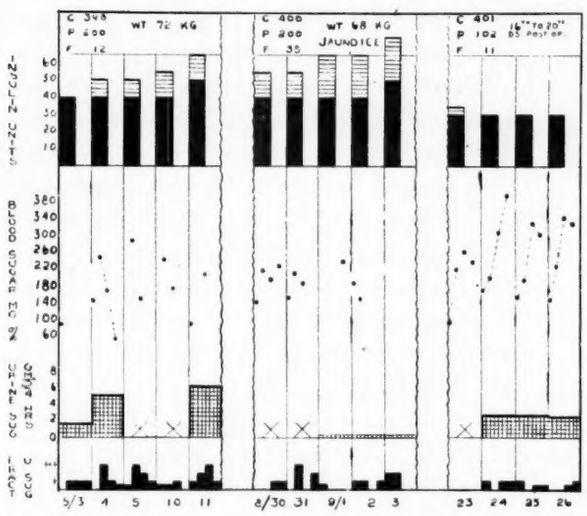


FIG. 3. *Insulin requirement before and after total pancreatectomy; operation September 7th; protamine zinc insulin indicated by solid bars, crystalline insulin by cross-hatched bars.*

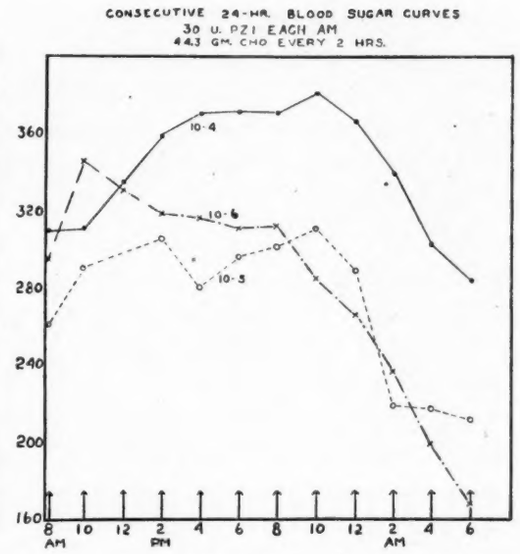


FIG. 4. *Legend above illustration.*

two-hour intervals throughout each twenty-four hours. It is apparent from Figure 4 that with the supply of food and insulin at constant levels, the blood sugar showed a definite downward trend during the night.

TABLE III

COMPARISON BETWEEN ACTUAL AND CALCULATED FECAL NITROGEN (GM./24 HRS.)

	10/24	10/25	Mean
N intake	15.98	15.98	15.98
N in urine	2.52	4.68	3.60
N in feces (calculated)	13.46	11.30	12.38
N in feces (actual)	12.34 (av.)	12.34 (av.)	12.34

Fasting Blood Sugar with Regular Insulin: It is well known that severely diabetic patients maintained on crystalline insulin, the last daily dose being given before supper, commonly exhibit marked hyperglycemia the following morning. The patient in question did not behave in this fashion, as shown by the data for October 21st to 26th. (Fig. 2.) This was the only period in which the patient refrained from eating during the night and when no interfering studies were being carried out. Diet, insulin dosage and activity were constant and the diarrhea was relatively so. It will be noted that with the exception of October 23rd, when the patient had received orange juice during the night for an insulin reaction, the fasting blood sugar on each day did not exceed 111 mg. per 100 ml.

TABLE IV

BASAL METABOLIC RATES AND RESPIRATORY QUOTIENTS

Age..... 53
Height..... 188 cm.
Diet..... C 400, P 101, F 99
Insulin..... 10-5-5
15–10–10

Date 1944	Wt. (Kg.)	Total Cal./hr.	B.M.R.*	R.Q.	Non-Protein R.Q.
Oct. 21.	56.9	52.9	−18	0.77	
		53.2	−18	0.79	
Oct. 24.	56.0	53.8	−17	0.80	
		53.3	−17	0.79	
Oct. 25.	55.9	53.0	−18	0.77	
		52.6	−18	0.80	0.793
Oct. 26.	55.9	54.5	−15	0.79	
		56.2	−13	0.79	0.792

* Mayo Foundation Standards

Intravenous Glucose Tolerance Tests: Glucose tolerance could be measured only by the intravenous technic, since the oral method led to prompt and profuse watery diarrhea. Such a test, performed on October 26th after the patient had been receiving only crystalline insulin three times daily, gave a curve which, though

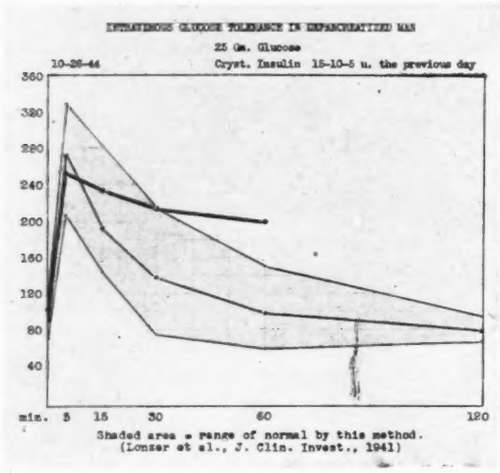


FIG. 5. *Legend appears on illustration.*

distinctly "diabetic," was less abnormal than in many cases of spontaneous diabetes. (Fig. 5.)

Respiratory Metabolism: Fasting total respiratory quotients were determined from October 21st to 26th, inclusive (Table IV), while the patient was taking a diet of C 400, P 101, and F 99 Gm. During this period the patient was given three daily doses of crystalline insulin, the last before supper. He received no protamine zinc insulin which, by its prolonged action, might have affected the fasting R.Q. The values obtained ranged from .77 to .80. An effort to measure the R.Q. after insulin had been completely withdrawn for several days was unsuccessful because of the patient's physical discomfort.

Non-protein R.Q. and the Metabolic Mixture: On October 25th, 4.68 Gm. of nitrogen were excreted in the urine. The following morning the non-protein R.Q. was .792. Calculations from these data and from the modified table of Zuntz and Schumburg, given by DuBois,[16] indicate that on this day the patient was deriving 9.4 per cent of his calories from protein, 27.7 from carbohydrate, and 62.9 from fat.

The *D/N ratio* of the urine was determined on December 7th and December 17th to 18th. On the first occasion the last dose of insulin was given December 3rd. On December 6th the patient consumed carbohydrate 156, protein 33, and fat 6 Gm. (810 calories). He received no nourishment from 8:00 P.M. on December 6th until 10:00 P.M. December 7th. The urine collected between 6:00 A.M. and 10:00 P.M. on December 7th contained 2.13 Gm. glucose and 0.88 Gm. nitrogen per 100 ml., representing a *D/N* ratio of 2.42.

On the second occasion the last dose of insulin was given December 12th. On December 16th the patient consumed only 6 Gm. carbohydrate (24 calories) and took no nourishment thereafter. The urine was collected by catheter from 11:00 A.M. December 17th, to 4:00 A.M. December 18th, when death occurred. This seventeen-hour specimen contained 4.20 Gm. glucose and 1.17 Gm. nitrogen per 100 ml., yielding a D/N ratio of 3.59.

TABLE V
SERUM AMYLASE

Date	Units
Mar. 21	68
Apr. 14	81
Sept. 7 Pancreatectomy	
Sept. 13	32
Sept. 14	9
Sept. 26	10
Oct. 17	66
Oct. 24	71
Dec. 5	35

Withdrawal of Insulin: On December 4th all insulin was withdrawn. On that day, the amount of sugar in the twenty-four-hour urine increased from less than 10 Gm. to 112 Gm., and on December 5th, 143 Gm. were excreted and the test for acetone was positive. The urine for December 6th or 7th contained 2.5 per cent glucose despite the fact that no food was eaten for twenty-four hours, and the test for diacetic acid became positive. On December 7th the serum carbon dioxide was 28 and chlorides 90.3 mM/L and the serum pH was 7.43. The patient had lost 4.6 kg. of body weight in three days and was very thirsty and uncomfortable. Insulin was then reinstituted with prompt relief of these symptoms. By December 12th the patient was in such suffering from recurrent carcinoma that it was decided to withdraw insulin as a terminal measure. The patient was now eating very little. Glycosuria again increased and ketosis this time appeared immediately, probably because of the preceding low intake of carbohydrate. On December 15th, 108 Gm. of glucose were lost in the urine and the patient became restless and irrational. Acetone and diacetic acid were now present in large amounts. On December 17th he was stuporous, the pulse

rose to 140 and respirations to 40 per minute; the blood sugar was 570 mg. per cent. Death occurred December 18th, after six days without insulin, in typical diabetic coma.

Miscellaneous Studies: Serum amylase (Table v), which was normal (68 to 81 units) before pancreatectomy, declined to 9 units one week afterward, but at the end of approximately six weeks had again returned to normal levels. These facts throw doubt on the hypothesis that the pancreas plays a major rôle in determining the amount of amylase in the blood and render uncertain the interpretation of such values.

There were no significant changes in values obtained throughout the patient's illness for serum CO_2, pH, Cl, Na, K, Ca, P or protein, except for a decline in Cl to 90.3 mM/L on December 7th after the first period of acidosis. No determinations of these substances were made after the final withdrawal of insulin.

COMMENTS

Certain features of this case require comment. The fecal volume after operation may have been influenced by factors other than the mere absence of the pancreas. For example, it was found at autopsy that the wall of the colon was diffusely infiltrated with carcinoma, which may have altered intestinal motility. At any rate, the amount of feces excreted daily was relatively enormous, ranging from 459 Gm. to 5,580 Gm. and averaging 1,500 Gm. to 1,800 Gm. Beazell, Schmidt, and Ivy[4] in a study of four cases of pancreatic achylia, found the average daily fecal weight to be 441 Gm. and the highest 706 Gm. In the present case, fecal solids were determined in the postoperative period only once, when they amounted to 281 Gm., or approximately five times the normal.[41] This compares with values of 80 to 120 Gm. found by Waugh et al.[56] in four cases of total pancreatectomy in man. In contrast to the experience of others,[4,56] the administration of pancreatin in our case was not very effective in controlling diarrhea, atropine giving more satisfactory results.

The increase in the frequency and amount of the stools following pancreatectomy was reflected in a marked increase in fecal nitrogen and fat. It is of interest that with the large loss of 12.34 Gm. of nitrogen in the stools (77 per cent of the amount ingested) on October 25th, the urinary nitrogen, as if in compensation, was only 4.68 Gm. per day. Average normal values for fecal and urinary nitrogen are 1 to 3 Gm.[4,15,32] and 10 to 15 Gm.,[15,32] respectively, per day. Beazell, Schmidt, and Ivy in a summary of reported cases of pancreatic achylia state that an average of 61 per cent of the ingested nitrogen was excreted in the feces. In their own cases, this value varied from 40 to 100 per cent, one patient losing 13.3 Gm. of nitrogen daily in the stools. In the Mayo Clinic series of total pancreatectomies[56] fecal nitrogen ranged from 4 to 8 Gm. per day. Fecal lipids in our patient amounted to 75.9 Gm. during one twenty-four hour period, or 77 per cent of the fat ingested. The feces of normal persons contain approximately 10 to 15 Gm. of fat each day.[4,52] In the literature dealing with pancreatic achylia, Beazell and his colleagues found an average of 62 per cent of the ingested fat excreted in the stools. In their own cases, with an intake of 112 Gm. of fat daily from 44.5 to 94 Gm. were lost in the feces, or an average of 66 per cent of the dietary fat. They state that absorption was materially improved by the administration of pancreatin. More closely akin to the present case are patients in whom the entrance of pancreatic juice into the intestine has been prevented by surgical operation, usually subtotal pancreatectomy. Whipple and Bauman,[57] in a study of three such patients maintained on a fat intake of from 75 to 100 Gm. per day, report that daily fecal fat varied from 3.2 to 81.2 Gm., representing excretion of from 3.2 to over 100 per cent of the ingested fat. The cases of total pancreatectomy reported by Waugh et al.[56]

lost from 36 to 48 Gm. of lipids per day in the stools with an intake of 70 to 100 Gm. It is to be pointed out, however, that in many cases absence of the external pancreatic secretion is compatible with practically normal fat digestion and absorption.[3,8,57]

It must be recognized that the diabetes in this case may have been influenced by certain factors which might render difficult a comparison with other forms of the disease. The absence of the pancreas undoubtedly impaired digestion and promoted diarrhea, thus tending to diminish hyperglycemia and insulin requirement. These tendencies were probably offset to some extent by the very high level of carbohydrate intake on which the patient was maintained. Furthermore, the direct entrance of food into the small intestine, owing to the absence of the stomach, may have resulted in an exaggerated response of the blood sugar to the ingestion of carbohydrate.[24] The possibility of adrenal cortical insufficiency due to the loss of the left adrenal would seem to be excluded by the patient's excellent postoperative recovery without replacement therapy and by normal values for serum electrolytes.

With due regard for these considerations, one may be permitted to comment on the fact that total pancreatectomy apparently failed to increase the severity of the preexisting diabetes. This could be explained logically if it were assumed that the original disease had been associated with complete destruction or functional failure of the islet tissue. Histologically, while most of the islets in the portion of the pancreas not involved by carcinoma appeared normal with routine staining methods, specific stains showed a very small number of beta cells. It could not be stated, however, that either the number or the activity of these cells was so diminished as to spell "total diabetes" in the patient. Unfortunately, assays for insulin content were not performed on the extirpated gland. If, on the other hand, some insulin were being produced before operation, it is difficult to understand the failure of the insulin requirement to rise afterward. Speculation might include the assumption of an extrainsular, "anti-insulin," factor which was removed by pancreatectomy. Of interest in this connection is the finding of Dragstedt[13] that partially depancreatized dogs have a higher requirement for insulin than totally depancreatized dogs. Young,[61] moreover, reports that when one of his dogs made permanently diabetic by injections of anterior pituitary extract was later depancreatized the insulin requirement was diminished. He states that this "may indicate that the acinar tissue of the pancreas plays a hitherto unsuspected rôle in carbohydrate metabolism." Similar results have been described by Thorogood and Zimmermann[53] utilizing dogs made diabetic with alloxan and subsequently depancreatized. The only evidence in man which points in this direction is the case described by Harvey[25] in which sub-total pancreatectomy in a previously nondiabetic patient resulted in diabetes necessitating 70 to 120 units of insulin per day. This is considerably in excess of the requirement of any human case of total pancreatectomy thus far recorded. In this institution the two patients who developed diabetes after subtotal removal of the gland exhibited only a very mild, and in one instance transient, form of the disease.[10] One other patient with diabetes has undergone total extirpation of the pancreas.[56] It may be significant that that patient, who had been taking 20 units of insulin per day, was found after operation to need the same amount, namely 40 units daily, as did the patient in the present case.

The relatively low insulin requirement of approximately 40 units per day is in the same range as that found in other cases of total pancreatectomy. Eight such patients, in addition to the present one, have been

reported.[23,35,46,56] Of these, three died within fifteen days of operation[23,46] so that an estimate of their true requirement in the absence of complications could not be made. In one of the three patients,[46] moreover, a remnant of pancreatic tissue was found at autopsy. The daily dosages in these cases were from 26 to 50 units, approximately. Of the remaining five patients, one[56] died 2.5 months and another[35] nine months after operation; while three[56] had been living eight, fifteen, and thirty-seven months, respectively, at the time of reporting. The insulin requirement in these five patients ranged from 26 to 40 units daily. It thus appears that totally depancreatized men require no more than about 40 units of insulin per day. Does it follow that the output of insulin by the normal pancreas must be of this order of magnitude? Previous estimates of the secretion of insulin by the normal human pancreas have ranged as high as 200 to 300 units per day.[47] Holm,[28] however, calculated on the basis of experiments in depancreatized dogs that the adult human pancreas, if the caloric requirement were fully supplied by sugar alone, might secrete approximately 48 units per day—a figure in closer agreement with the findings in pancreatectomized patients. The observations of Dragstedt,[13] Young[61] and Thorogood and Zimmermann[53] referred to above are pertinent to the problem. The latter, in discussing their finding that alloxan treated dogs require more insulin before than after pancreatectomy, point out that since alloxan attacks the beta cells specifically, diabetes thus produced represents a pure (and presumably complete) insulin deficiency. The fact that the insulin requirement of these animals is much reduced by pancreatectomy suggests that this operation removes a substance either in the alpha cells[53] or in the acinar tissue which is antagonistic to insulin, and that the amount of the hormone produced by the normal dog's pancreas can be estimated more truly from the requirement in alloxan diabetes than in the diabetes of complete pancreatectomy. To what degree this reasoning can be applied to man cannot be stated since strictly comparable experiments have not been carried out in that species. At any rate, the possibility must be recognized, on the basis of the observations on pancreatectomized patients, that in any case of diabetes requiring more than about 40 units daily, an insulin antagonist of some sort may be at work. "Insulin resistance," therefore, may begin at a much lower level of insulin requirement than heretofore believed.

The contour of the twenty-four hour glycemic curves confirms Möllerström's observations[40] concerning the diurnal fluctuation of the blood sugar in diabetic patients and demonstrates that this phenomenon can occur without variations in the supply of insulin and food. The findings do not constitute proof of his hypothesis, probable though it may be, that the liver is responsible for such fluctuations. The normal fasting blood sugars of October 21st to 26th while the patient was receiving crystalline insulin, and the relatively good tolerance for intravenous glucose are not characteristic of most diabetic patients who require 40 units of insulin per day. It cannot be stated on the basis of one case, however, that such behavior is typical of the depancreatized man, and its explanation in the present instance is not clear.

The respiratory quotients of .77 to .80 are definitely but not far below the generally accepted average of .84 for normal individuals. They are, however, considerably above the R.Q. of .70 exhibited by the totally depancreatized dog not receiving insulin.[43] Values for severe human diabetes obtained before the discovery of insulin are given by Benedict and Joslin[5] as ranging from .69 to .77 with a mean of .74; by

Gephart, Aub, DuBois and Lusk[21] from .66 to .97; and by Wilder, Boothby and Beeler[58] from .66 to .74. Most of these quotients approximate the R.Q. of pure fat oxidation. In our patient the total respiratory quotient would indicate that foodstuffs other than fat, presumably including carbohydrate, were being oxidized in the absence of endogenous insulin. Supporting this probability are calculations based on the non-protein R.Q. and the urinary nitrogen which show that on one occasion 9.4 per cent of the calories were being derived from protein, 27.7 per cent from carbohydrate and 62.9 per cent from fat. Comparable figures for normal individuals are indicated by DuBois, who states, "Under ordinary conditions . . . 10 to 20 per cent of the calories come from protein and 20 to 70 per cent from carbohydrate."[16] By these standards, the number of calories furnished by both carbohydrate and protein in the present case was lower than the normal average but not below the normal minimum. It is fair to conclude that the oxidation of carbohydrate in the complete absence of the pancreas was by no means abolished fourteen hours after the injection of insulin.

The D/N ratios of 2.42 and 3.59 are of the same order of magnitude as those which have been repeatedly found for the depancreatized and the phloridzinized dog,[42] respectively, and are in the same range as those reported by earlier authors in human diabetes.[2,21,22,34,36] It is possible that the ratio of 2.42 obtained December 7th is too high because of the pouring out of glucose from the glycogen reserves of the days immediately preceding.[6] The fact, however, that insulin had been withdrawn three days previously, with the consequent loss of from 112 to 143 Gm. of glucose per day in the urine, would suggest that the glycogen stores had undergone considerable depletion before the day in question. This criticism is probably not applicable to the ratio of 3.59 obtained December 17th and 18th. On this occasion, insulin had been withdrawn four days previously and the intake of food had been practically zero (6 Gm. carbohydrate) on the day immediately preceding the observation. Cyril K. in the case described by Gephart, Aub, DuBois, and Lusk,[21] showed ratios of 2.76 and 2.65 on two days of fasting which were preceded by two days of a practically carbohydrate-free diet, and in the case of William G., Allen and DuBois[2] found ratios from 2.28 to 3.82 when the patient was being fed almost nothing but protein. The depancreatized man then resembled severely and spontaneously diabetic patients and pancreatectomized and phloridzinized dogs in being able to convert roughly half his metabolic protein to carbohydrate.

Again reminiscent of the depancreatized dog are the promptness and extent of the ketosis, glycosuria, dehydration and loss of weight which followed the withdrawal of insulin. Many severely diabetic patients have themselves inadvertently proven that failure to take insulin may be fatal. An unusual combination of circumstances in the present case permitted the experimental verification, if indeed any were needed, of this fact. The patient's death in typical diabetic coma six days after the deliberate abandonment of treatment constitutes, so far as we are aware, the first instance in which the essentiality of a hormone for human existence has been demonstrated by the removal of the gland manufacturing that hormone and the subsequent withholding of replacement therapy.

The question of whether total pancreatectomy in man results in lipocaic deficiency cannot be answered by available data. The evidence of such deficiency in dogs, according to Dragstedt[14] includes a fatty liver and a decline in both insulin requirement and serum lipids. In the patient under discussion

autopsy showed fatty degeneration of the liver, but this could have resulted from inanition and the terminal diabetic acidosis. Insulin requirement did not change appreciably. As shown in Table VI, the serum lipids, after the first postoperative month, fell from 20 to 30 per cent below the value found five days after operation, but never reached subnormal levels. The large amounts of pancreatin which the patient received for long periods of time may have served to prevent manifestations of lipocaic deficiency. It is of interest, however, that one of the patients reported by Waugh et al.[56] refused to take any lipotropic substances such as raw pancreas, lipocaic, lecithin and choline, yet suffered no decrease in serum lipids as late as thirty-seven months after operation and was feeling well and had no complaints.

SUMMARY

Pancreatectomy, the completeness of which was established at autopsy, was performed for carcinoma in a patient who was already diabetic and had chronic diarrhea. The stomach, duodenum, spleen, and left adrenal were also removed. For approximately three months the patient remained in sufficiently good condition to permit metabolic studies. Loss of the pancreas led to a marked increase in diarrhea, the daily fecal weight on one occasion being 5,580 Gm., even though the patient was receiving powdered pancreas in large amounts. Atropine was more effective than pancreatin in controlling fecal volume and its effect was augmented by a sharp reduction in dietary fat. Intestinal absorption of both fat and protein, already less than normal before operation, was strikingly diminished thereafter. The large loss of nitrogen in the feces (12.3 Gm. daily) was accompanied by the relatively low urinary loss of 4.68 Gm. per day. Analyses of food and excreta showed a slightly positive calcium and phosphorus balance, despite the severe diarrhea.

Extirpation of the pancreas was not followed by any increase in the requirement for insulin which, with a diet containing 400 Gm. carbohydrate, averaged about 40 units per day. Sensitivity to insulin was marked, the patient experiencing frequent hypoglycemic reactions. With the patient receiving constant feedings every two hours and a constant supply of insulin derived from the daily injection of protamine zinc insulin, the blood sugar exhibited a definite diurnal pattern, the lowest values occurring during the night. The phenomenon is presumably related to rhythmic variations in the activity of the liver. When the patient was maintained on three injections of crystalline insulin per day, the last dose being given before supper, the fasting blood sugars were essentially normal. This is contrary to the usual finding in severe, spontaneous diabetes. Also at variance with the behavior of such patients was the response in the present case to intravenously administered glucose, the resultant blood sugar curves being less "diabetic" than might be expected. The postabsorptive respiratory quotients varied from .77 to .80, values which are considerably higher than those for totally depancreatized dogs or severely diabetic human beings. Of the total calories derived from the metabolic mixture, 27.7 per cent came from carbohydrate, 9.4 per cent from protein and 62.9 per cent from fat. When insulin and food were withheld, the D/N ratio of the urine was 2.42 and 3.59 on two occasions, respectively. Permanent withdrawal of insulin resulted within six days in the death of the patient in diabetic coma. Values for serum amylase fell to low levels shortly after operation, but later returned to normal. One month after removal of the pancreas, serum lipids had declined from 20 to 30 per cent below the immediate postoperative value, but they never reached subnormal levels. Pancreatectomy produced no striking changes in serum carbon dioxide,

pH, Cl, Na, K, Ca, P, or in plasma proteins. The considerable loss of nutriment through diarrhea may explain certain apparent differences between the diabetes in this case and the spontaneous disease of ordinary diabetic patients.

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Clearance of Inulin, Diodrast, Chloride and Phosphate under Mercurial Diuresis*

Intensive Study of a Patient in Severe Cardiac Failure

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THE purpose of this study was to trace as closely as our present technical facilities would permit, the course of a patient who was hospitalized in acute cardiac failure. The application of clearance tests, repeated at intervals of a week or two throughout his hospital stay of ten weeks, was chosen with the hope of obtaining information concerning the behavior of the functional renal components in extreme decompensation and under the influence of mercurial diuretics.

The use of inulin had manifest advantages, since its passage through the glomerular filter in the same concentration as in the circulating plasma, and its conduction through the tubules as an inert, non-metabolized substance, had been well established.[1,2] The interval determination of its clearance value offered us, therefore, the filtration rate at moments during the clinical course of the patient when he was either suffering from marked fluid retention or was passing unusual volumes of urine. Furthermore, since the ratio of concentration of inulin in the circulating plasma and inulin in the urine could be influenced only by changes in the fluid volume by withdrawal of water by the lining cells of the proximal tubules, that fraction, or the U/P inulin, furnished us with an index to the amount of water reabsorbed and hence an insight into the function of the proximal segments. We were thus enabled to consider chloride not simply in terms of urine concentration but in terms of water actually reabsorbed. The site of chloride resorption has also been located with some certainty in the distal tubules,[3,4] and the ratio of urine chloride to serum chloride, considered in relation to the U/P inulin or the reabsorbed water, might be thought of as a function test of the distal tubules.

Diodrast was added to the infusion fluid because its mode of excretion by the cells of the tubules supplied useful information concerning the effective renal blood flow,[1] a factor which required investigation in a patient whose venous pressure was abnormally elevated.

CASE REPORT

The subject was a thirty-five-year old white male who entered Passavant Hospital on September 9, 1942, complaining of dyspnea, orthopnea, edema, marked gain in weight and pain in the legs. He had had "inflammatory rheumatism" in 1918 and had first given evidence of cardiac decompensation in 1938. From that time he had been in bed or inactive for long periods. Physical examination revealed a young man in acute distress, in whom edema was so extreme that the garments had to be cut from his lower extremities. A harsh systolic murmur was heard over apex and base, with pre-systolic and diastolic murmurs in the third and fourth left interspaces. The heart was markedly enlarged; coarse wet râles were heard in the bases and the liver was very large and tender.

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Edema was marked over the abdominal wall which also showed cyanosis below the level of the heart. The systolic blood pressure was 196, the diastolic 130. The erythrocyte count was 4,250,000, the hemoglobin 14.0 Grams. The leucocyte count was 7,150. Urine analysis showed albumin, two-plus, with scattered hyaline casts. The blood urea nitrogen was 19.0 mg. per cent, and the carbon dioxide combining power, 25.5 volumes per cent. The total protein was 6.65, with 3.92 Grams of albumin. The two-meter chest roentgenogram showed a mitral and an aortic configuration with a total cardiac enlargement of over 30 per cent. The electrocardiogram showed a right axis deviation with marked slurring of the QRS complexes and deformity of the T waves.

The acid-base balance was promptly adjusted, and the initial weight of 218 pounds was brought down to 197 by bed rest and diuretic management before clearance tests were performed.

The tests were done in the morning with the patient in the fasting state. The intake of fluids was at no time restricted, and the patient was encouraged to drink water according to thirst. Fluids were not forced in preparation for the tests. The usual technic for the inulin clearance was employed, the inulin and diodrast being added to sterile physiological saline solution. Catheters were introduced and the urine specimens were collected by rinsing the bladder with sterile water. The blood for the chloride determinations was taken under oil and estimations were done on serum and quoted in terms of sodium chloride. Three or four clearance periods were determined, the intervals ranging from fifteen to thirty minutes. The inulin, diodrast, chloride and phosphate were analyzed concomitantly, the method of Sendroy[5] being employed for the chloride, that of Corcoran and Page[6] for the inulin.

RESULTS

The results have been tabulated in Table I in which the volume of urine in cc. per minute, inulin clearance, diodrast clearance, chloride and phosphate clearance, U/P inulin, U/P chloride and U/P phosphate have been listed, with the dates upon which

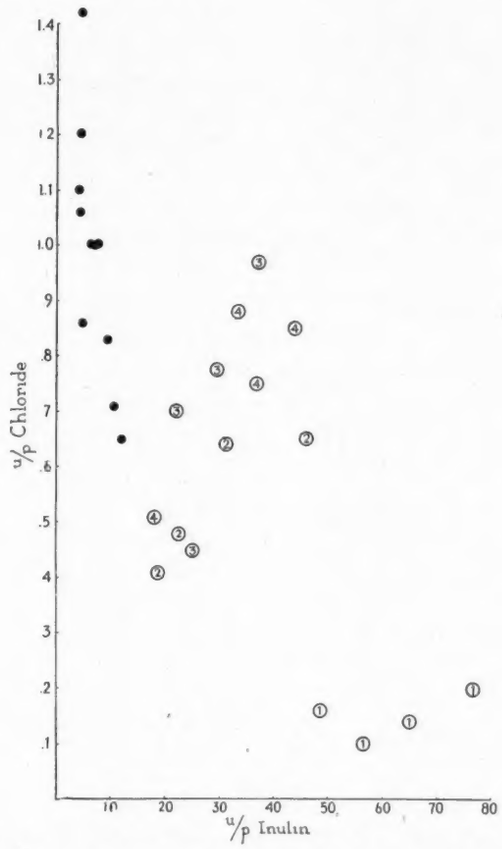

FIG. 1. *Chloride excretion in patient with severe heart failure (A. Z.). Circles indicate clearance periods without mercupurin. Dots indicate clearance periods in which mercupurin was given prior to the test.*

the tests were performed. Since the clinical improvement of the patient and the loss of the extreme edema which characterized his condition on admission introduced factors which required assessment, his weight on the morning of the test is also given.

The filtration rate as represented by the clearance of inulin was found to vary but slightly from test to test and the average clearance, three weeks after admission to the hospital, was almost identical with the final determinations just prior to discharge after the loss of fifty-two pounds of edema fluid. It was evident, furthermore, that diuresis with mercupurin intravenously administered, failed to alter significantly the filtration rate, even with a urine volume of 19.8 cc. per minute.

TABLE I*

Mercupurin	Volume: Cc. per Min.	Inulin Clearance	Diodrast Clearance	Chloride Clearance	Phos. Clearance	U/P Inulin	U/P Chloride	U/P Phos.	Wgt.
With Mercupurin									
Oct. 16, 1942	6.6	69.1	157.5	4.68	22.0	10.5	.71	3.34	204
	7.0	65.4	147.8	5.89	24.7	9.3	.83	3.51	
	4.1	48.8	107.3	2.64	16.7	12.0	.65	3.79	
Nov. 10, 1942	19.8	77.0	177.5	14.20	31.9	4.7	.86	1.92	
	13.4	83.0	154.0	13.70	26.8	6.2	1.02	1.99	176
	8.4	66.0	121.8	8.60	21.3	7.8	1.02	2.54	
	10.9	75.4	141.4	10.70	23.9	6.9	1.00	2.20	
Nov. 16, 1942	10.5	50.6	147.8	15.60	35.6	4.8	1.43	3.40	
	11.8	51.7	140.9	14.50	30.5	4.3	1.21	2.56	173¼
	15.5	61.8	179.2	17.20	36.8	4.0	1.11	2.41	
	17.3	69.4	199.1	18.40	37.1	4.0	1.06	2.16	
Without Mercupurin									
Oct. 8, 1942	.8	45.5	119.0	0.12	7.24	65.0	0.14	10.33	
	1.2	57.7	135.0	0.19	10.34	48.5	0.16	8.60	197
	.7	53.7	117.0	0.14	10.08	76.8	0.20	14.10	
	.5	30.8	55.3	0.09	3.98	56.8	0.10	7.05	
Nov. 20, 1942	2.3	36.2	102.0	0.80	10.2	18.3	0.41	5.17	
	1.6	36.8	98.8	0.79	9.9	22.6	0.48	6.16	169¾
	1.1	35.9	98.4	0.72	9.5	31.6	0.64	8.40	
	1.1	59.8	157.6	0.71	10.0	46.7	0.65	9.18	
Nov. 30, 1942	2.2	54.0	121.6	0.96	12.3	25.2	0.45	5.74	
	1.5	55.7	131.9	1.44	13.7	37.4	0.97	9.21	173¾
	2.5	55.4	124.1	1.74	14.3	22.1	0.70	5.71	
	1.8	53.0	186.7	1.38	12.8	29.5	0.77	7.15	
Dec. 11, 1942	3.3	60.3	203.0	1.71	15.2	18.0	0.51	4.5	
	1.7	64.7	191.0	1.65	13.2	36.9	0.75	7.5	165¾
	1.7	54.9	176.0	1.46	13.0	33.2	0.88	7.9	
	1.4	64.0	169.0	1.24	12.3	43.9	0.85	8.4	

* Data obtained from patient (A.Z.) in severe cardiac failure and under mercurial diuresis.

Somewhat more variation may be noted in the diodrast clearances; and the average of those periods completed on December 11th, when compensation had been more nearly restored, was higher than in previous tests. The individual periods also present fluctuations beyond what we have found under similarly controlled conditions in individuals with normal cardiovascular systems. Improvement in cardiac compensation, however, did not produce the consistent increase in diodrast clearance which improved circulation in the kidneys might have led one to anticipate. No correlation is traceable between the diodrast clearance and the large outputs resulting from mercurial diuresis.

With respect to the clearance of chloride, at least two factors may be seen to have influenced the results, the most striking of which is the effect of mercury. The more copious the diuresis, the higher did the chloride clearance rise. This fact is in contrast with chloride clearances run in our laboratory on normal individuals with varying outputs, in which the clearance was found to vary only within a range of 0.5 to 3.0 cc. per minute, regardless of the urine volume. In order to analyze these figures in terms of tubular resorption, the U/P inulin was selected as an index to water reabsorbed and plotted against the U/P chloride. (Fig. 1.) This graph suggests the second factor which influenced the chloride data, namely, the progress of the patient toward compensation. In order to make this point clear, the

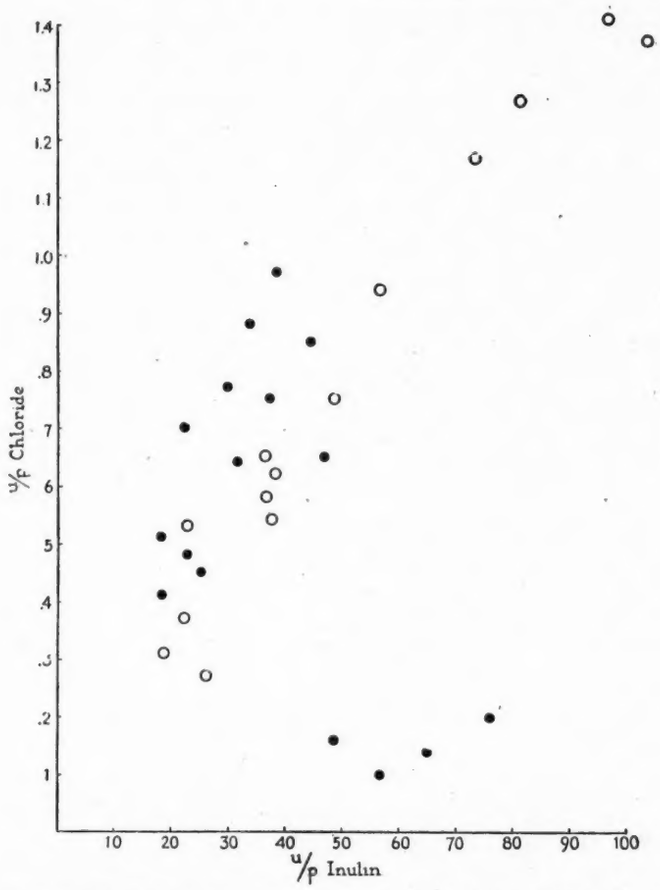

FIG. 2. *Chloride excretion in patient with heart failure. Dots indicate clearance periods on A. Z. Circles indicate control series performed on normal subject, J. P. No mercupurin was used in these determinations.*

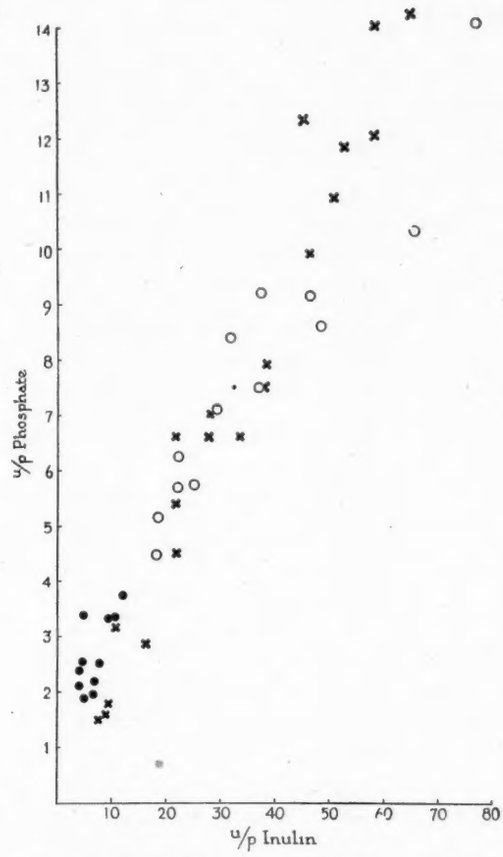

FIG. 3. *Phosphate excretion in patient with heart failure. Circles represent A. Z., after administration of mercupurin. Crosses indicate control series on subject, J. P.*

periods completed on a given day have been marked by a number, the numbers being arranged to indicate a time sequence. The clearance periods performed without the use of mercupurin show a wide scatter and have been plotted on a separate graph against those obtained from a normal subject (Fig. 2), in terms of U/P inulin and U/P chloride.

The phosphate clearance may be seen to bear a relationship to urine output, but a quantitative relationship does not appear to exist between phosphate and chloride. Plotting again in terms of U/P inulin, however, the results obtained under the influence of mercurial diuresis are found to follow pretty closely the curve described by periods in which mercupurin was not employed. This graph has in turn been combined with one taken from a normal individual without the administration of medical diuretics. Comparison of the regression lines shows the cardiac patient a little to the left, particularly in the mercupurin periods of low U/P inulin ratio. (Fig. 3.)

COMMENT

The variable handling of water and response to diuretics characteristic of cardiac failure is a clinical commonplace. The present study, however, enabled us to ascertain that in this subject, at least, the variations in fluid and chloride balance did not occur as a result of changes in filtration rate or circulatory conditions, as reflected in the

diodrast clearance, throughout the period under investigation. The locus of action appears rather to lie in the proximal tubules. The filtrate has been formed as usual and at the same rate, regardless of the volume of urinary output. It could be proposed then, that the diminished output incident to the positive fluid balance of acute or chronic decompensation is a result of a specific change in reabsorption by the proximal tubules, similar to the influence of antidiuretic hormone. If such may be accepted as a working hypothesis, the functional defect characteristic of heart failure would be thought of as an altered output of antidiuretic hormone or as an altered threshold of renal tubular response to antidiuretic hormone in normal concentrations.

If we proceed to examine the fate of chloride in the distal tubules, the evidence is found to be inconclusive, since per unit of water reabsorbed in the proximal tubules, the U/P chloride shows no single trend. On October 8th the clearance periods yielded a high U/P inulin ratio but the chloride was far lower than normal. Later, however, although the U/P ratio of inulin and chloride still bore an irregular relationship to one another, they were roughly scattered about the regression line of the control studies and fell, if anything, somewhat to the left, thus indicating a tendency to increased U/P chloride at any given U/P inulin. The inconsistency of this patient's behavior toward chloride is difficult to account for, and further studies would be desirable on other decompensated patients. It may be pointed out only that the distal tubules appear to be specifically affected, and that the phosphate does not share the influence of the causes determining chloride disposal.

Turning now to the lower U/P inulin ratios, the effect of mercupurin on chloride is seen to be dramatic. In earlier papers[7,8] we showed that in a normal subject, the more closely the urine composition approximated the glomerular filtrate the lower the U/P chlorides, so that the projected regression line of U/P inulin against U/P chloride passed through zero. Such a figure could be regarded as a graphic presentation of the threshold theory. In our patient, on the contrary, the lower the U/P inulin, the higher the U/P chloride; the less the proximal tubules operate to withdraw water from the current of filtrate the less also do the distal tubules act to reclaim the chloride.

The failure of the diuretic to produce a similar effect on phosphate excretion suggests either that phosphate is handled by other tubular cells or that the effect is through a specific agency capable of affecting one out of several functions of identical cells.

CONCLUSIONS

1. Degrees of oliguria associated with cardiac decompensation were found to be unassociated with a decreased filtration rate or with a substantial or consistent decrease in effective renal blood flow.

2. Relations between the U/P ratio of inulin and that of chloride were variable, and did not describe the straight line which is characteristic of the normal subject. Such variations were found only to a slight degree in the case of phosphate.

3. The administration of mercupurin resulted in a large increase in U/P chloride at all U/P inulin ratios. This was not paralleled by a proportionate increase in U/P phosphate. It is, therefore, probable that mercupurin exercised a specific effect upon chloride disposal and that the site of such effect was the distal tubules.

4. The diuresis resulting from mercupurin was not correlated with an increased filtration rate, and circulatory conditions in the kidneys as indicated by the diodrast clearance were variable and described no definite trend. The site of action of mercu-

purin was, therefore, concluded to lie in the proximal tubules.

5. Comparison of U/P inulin and chloride ratios in this subject with those collected from normal subjects indicated that, while in the normal subjects water and chloride are dealt with in such fashion that the plotted data form a regression line passing through zero, under the present experimental conditions this physiological pattern breaks down and the graph suggests a simultaneous reanalysis of both proximal and distal tubules with respect to water and chloride.

SUMMARY

A patient in severe cardiac decompensation was subjected to clearance tests of inulin, diodrast, chloride and phosphate over a period of eight weeks. The urinary output, daily weight and clearance figures, together with the U/P ratios of inulin, chloride and phosphate were tabulated. The U/P chloride was plotted against the U/P inulin in order to assess the reabsorption of chloride in the distal tubules in terms of water reabsorbed by the proximal tubules. The same was done in the case of phosphate.

Similar determinations were made under conditions resulting from the administration of mercupurin, and the data were plotted and compared with data drawn from experiences with normal individuals in varying degrees of water diuresis.

Evidence was found to support the idea that the oliguria of cardiac decompensation is not the function of a decreased filtration rate, and that the large outputs associated with mercurial diuresis are not the results of an increase in filtration rate. It, therefore, appeared probable that the fluid retention of cardiac decompensation should be considered as referring directly to the renal tubules, and that the action of the mercurial diuretic was first on the proximal tubules and second and specifically upon the behavior of the distal tubules toward chloride.

Grateful acknowledgment is made to Dr. A. S. Alving for his generous help in the preparation of this paper.

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Chrysotherapy in Rheumatoid Arthritis*

A Three-year Study of 142 Cases

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THE use of gold compounds is now an established form of therapy for rheumatoid arthritis. Most men working in this field agree that a significant number of patients respond favorably to gold, that this number is greater and that the response of the individual patient is more favorable with chrysotherapy than with any other single form of treatment.[1] The prevalence of toxic reactions from gold has been a grave deterrent to its use. Thus far, reports on its efficacy have been concerned with the immediate response to therapy. It is the purpose of this paper to present the results of chrysotherapy in patients with rheumatoid arthritis from the vantage point of a three-year follow-up.

Material. These patients were studied and followed in the clinic and on the wards of the Presbyterian Hospital. The diagnosis of rheumatoid arthritis was based on the usual clinical and laboratory data, including *x*-ray, sedimentation rate and agglutination with group A hemolytic streptococci.[2] In all patients included, the diagnosis was concurred in by at least three internists. Extra care was used to exclude all cases of subacute rheumatic fever in which the prognosis is favorable without the use of chrysotherapy. The period covered in this report includes the years 1939, 1940, 1941 and half of 1942. The follow-up study was made in the fall of 1945 and thus the minimum period between gold administration and this follow-up is over three years. The group included only those patients who received ½ Gm. or more of gold compound, which has been considered to be an adequate amount. Patients who were unable to tolerate even this amount because of toxicity or who failed to continue treatment for any reason are not included. Using these criteria in that time, we treated 152 patients with rheumatoid arthritis with gold. We have adequate follow-up records on 142 of these patients. The ten on whom the data are inadequate had moved from the vicinity of the hospital and efforts to trace them have been unsuccessful. Thus this report is concerned with 142 patients with rheumatoid arthritis who have been treated with gold compounds and subsequently observed for at least three years. The group is, we believe, a representative one, comprising 74 per cent females. The age of onset of symptoms of arthritis ranged from sixteen to eighty years with a median of thirty-nine years. The median duration of symptoms before institution of chrysotherapy was four years. Thirty-seven per cent had a negative agglutination with group A hemolytic streptococci which is about average in a large group.

Immediate Response to Treatment. The immediate response to therapy is of a type which is generally accepted. We have divided the results into subjective response and objective response. In all but eight patients these two categories are in agreement. In these eight, the subjective response was marked and the objective only slight. Using the subjective response, 55 per cent showed

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marked improvement, whereas using objective response 50 per cent showed marked improvement. Eleven per cent showed no improvement. In the remainder the improvement was definite but not startling.

Type of Gold. Three forms of gold compounds were used, myochrysin,* solganol B oleosum† and calcium aurothiomalate.‡ Seventy-two patients (50 per cent) received myochrysin, fifty-one (35 per cent) solganol, and nineteen (15 per cent) calcium aurothiomalate. Table I shows the results obtained with these three preparations. The differences are not statistically significant.

TABLE I
RELATION OF DRUGS USED TO THERAPEUTIC RESPONSE AND TOXICITY IN PATIENTS INCLUDED IN THIS SERIES, ALL OF WHOM WERE GIVEN AT LEAST ½ GM. OF GOLD COMPOUND

Drug Used	No. of Patients	Not improved		Improved		Significant Toxicity*	
		No.	Per Cent	No.	Per Cent	No.	Per Cent
Myochrysin	72	4	5	68	95	28	39
Solganol B Oleosum	51	8	15	43	85	16	31
Calcium aurothiomalate	19	2	10	17	90	4	21

* Significant toxicity is an arbitrary designation which includes all patients who developed a pruritis, rash, stomatitis, albuminuria or blood dyscrasia lasting more than one month.

Toxicity. Significant toxicity, that is a reaction such as dermatitis, or albuminuria of a duration of more than a month, followed the use of each drug. This is also shown in Table I and again the differences are not statistically significant. Of interest is the fact shown in Table II that significant toxic reactions following the use of gold compounds are related to the duration of the disease before the institution of such therapy. Reactions were more than twice as frequent in the patients who had had their disease over ten years as in those who had had the disease for less than one year. The dermatitides persisted for from one month to three years with a median duration of three months. Severe albuminuria lasted for one month to two years with a median duration of four months. Two deaths* occurred which could be attributed to the treatment, one due to aplastic anemia, the other to thrombocytopenic purpura. Two deaths occurred from other causes and could not be attributed to the use of gold, one following empyema of the gallbladder and the other a cerebral accident in an eighty-one-year old man.

Long-term Response to Treatment. The term "cure" has been used in describing the response of a patient with rheumatoid arthritis to gold. Viewed over a three- to four-year period, it becomes obvious that such a term seldom, if ever, should be used.

Eleven per cent of these patients showed no improvement with gold. Our experience would indicate that if a patient shows no response to 2,000 mg. of gold compound, further use of gold will bring about no improvement. Some of our patients have received 3 to 4 Gm. of gold compound with no improvement.

Thirteen per cent of the total group are still without symptoms of active rheumatoid arthritis from forty-five to seventy-eight months after the last injection of gold. However, 75 per cent did relapse. These relapses took place from one to fifty-eight months after the cessation of treatment. In general, the relapse was less severe than the original arthritis, but in all it was definite. The response to therapy with gold usually follows a clear-cut pattern and the relapse follows a similar pattern in reverse. Under treatment, the first symptom to subside is

* Merck & Co.
† Schering Corp.
‡ Merck & Co.

* Gold has been used in this clinic for six years and we have treated 460 patients with gold compounds. These two deaths are the only ones we have had. The last received gold in 1942. Thus the treatment mortality in this group of 142 patients is misleading and corrected it should be 2 out of 460 or 0.4 per cent. The patient who died of aplastic anemia had several factors which might also have contributed, viz., carcinoma of the cervix which had been treated with radiotherapy, and syphilis treated with arsenic and bismuth. At the present time, we would not give such a patient gold therapy.

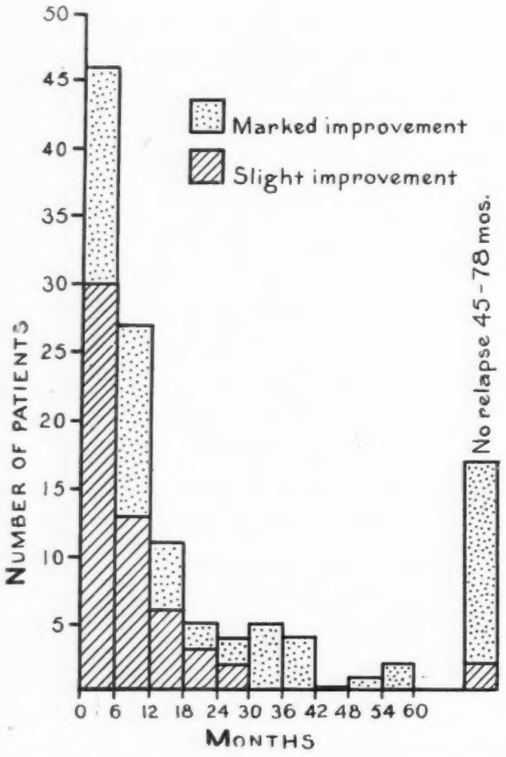

FIG. 1. *The month during which relapse occurred following cessation of gold therapy. It is to be noted that there is a tendency for patients with marked improvement to relapse at a later date than those with slight improvement.*

pain, the last stiffness. During a relapse, the first to reappear is stiffness to be followed later by pain. Swelling, redness and heat are variable. Generally, the sedimentation rate, if elevated, falls slowly but in a relapse the sedimentation rate may rise quite precipitously. The relapse rate bears no relation to the duration of the disease prior to therapy. Table II shows the percentage of relapses in the various groups in relation to the duration of the disease. The time of relapse bears a closer relationship to the type of improvement achieved on the first trial with gold compounds. Thus of the fifty-four patients showing slight objective improvement, a relapse occurred in one to thirty months, with a median of five months. In the group of fifty patients showing marked improvement (really arrest), a relapse occurred in one to fifty-eight months, with a median of eleven months. Two patients showing slight improvement and sixteen showing marked improvement have not relapsed at this writing. This is shown graphically in Figure 1.

Factors which account for relapse are not clear The eighteen patients who have not relapsed at this time have been followed from forty-five to seventy-eight months. Only nine of these have been followed sixty months or more and we have three patients who had definite relapses in their fifth year after treatment had ended. Thus only nine patients of the group or 6 per cent could be classified as five-year cures. This number is too few to be considered significant. In general, one should expect relapse in a patient with rheumatoid arthritis who has had a remission with gold.

It is a fair generalization to state that the relapse is not as severe as the original disease. It is of great importance to realize that the patient who relapses has an excellent chance of improving again on chrysotherapy. This is shown in Table III. Because

TABLE II
RELATION OF DURATION OF DISEASE TO THE DEVELOPMENT OF (1) TOXICITY, (2) THE RELAPSE RATE

	Duration of Disease Before Institution of Gold					
	Less than 1 Yr.	1–2 Yr.	3–4 Yr.	5–9 Yr.	More than 10 Yr.	Total
No. of patients	21	45	34	21	21	142
Per cent in whom significant toxicity developed	19	29	38	39	48	33
Per cent who relapsed	76	73	70	76	72	75

TABLE III
RESULTS WITH SUBSEQUENT USE OF GOLD

Type of Improvement on First Course	Not Improved Again (Per Cent)	Improved Again (Per Cent)	Not Tried (Per Cent)
Slight	24	45	31
Marked	4	74	22

of various factors including toxicity, 27 per cent received no further gold after they had relapsed. Of the remainder (seventy-seven patients) 80 per cent improved again on the administration of gold. If this group is further broken down into those who showed slight and marked improvement with the original course, 95 per cent of those showing marked improvement improved a second time, whereas only 66 per cent of those showing slight improvement, improved again. Thus, if a patient shows marked improvement after the original treatment with gold compound, he will relapse, but will probably improve again on subsequent gold compound therapy. With this in mind, we have now instituted a program of maintenance doses whereby a patient continues to receive gold at regular intervals indefinitely. This is still under trial and no definite schedule has been worked out, but we feel that a severe and disabling relapse can be prevented. At present, after the initial course of gold, we are using a maintenance dosage of 50 mg. every two or three weeks.[5]

The mechanism of the action of gold in the treatment of rheumatoid arthritis is still unknown. Various explanations have been propounded, including the bacteriostatic effect of gold,[3] and none are satisfactory. Freyberg[4] has shown that gold is excreted in the urine in measurable amounts for as long as ten months after cessation of therapy and the median month of relapse for the group is seven months. Thus, it is possible that there is a therapeutic level of tissue gold which must be maintained in order to keep in abeyance the process which is the cause of activity in rheumatoid arthritis.

Psoriasis Associated with Rheumatoid Arthritis. Eight per cent of the 142 patients had accompanying psoriasis.* This group has certain features which set it apart from the group as a whole. Similarities were the sex distribution (80 per cent females); the age of onset of arthritis (sixteen to forty-one years, with a median of thirty); the duration of the disease (a median duration of three years); and toxic reactions which appeared in four, or 36 per cent. However, dissimilarities were striking. The agglutination with group A hemolytic streptococcus was positive in only one of these 11 cases. The response to therapy was far from satisfactory. One is still well 68 months after the last gold injection. Four, or 36%, showed no improvement, and only 2, or 18%, showed marked improvement. The relapse rate and response to subsequent chrysotherapy were comparable to the group as a whole.

Agglutination with Group A Hemolytic Streptococcus. Since 1931, agglutination with group A hemolytic streptococcus[2] has been performed in this clinic on sera of all patients with rheumatoid arthritis. In the eight years, 1931 to 1939, under the usual conservative treatment, we had observed a change from positive to negative in only one patient. Since the advent of chrysotherapy in the three and one-half years covered in this report, seventeen patients have changed from positive to negative.

COMMENTS

A representative group of patients with rheumatoid arthritis who have been followed for at least 3 years shows that the disease process can be held in check in a large number by the use of gold compounds. The treatment is attended by a definite number of severe and disabling toxic reactions. That gold is not a curative agent is, we believe, amply demonstrated. There is strong evidence that it influences some system whereby the activity of the disease process is diminished. It is suggested that the excretion of gold is followed by a renaissance of activity of this process. The nature

* The psoriasis antedated the arthritis in six patients, thirteen to three years, a median of six. The arthritis antedated the psoriasis in four patients, four to one years, with a median of two. Psoriasis and arthritis appeared simultaneously in one patient.

of the process is not understood and unfortunately no direct light is thrown upon this problem by the data presented here. However, we do have some indirect evidence. The amount of gold injected is small, an average of 1,250 mg. of the compound, and the response is striking. One may presume that the gold inhibits some active process or system. When the gold is excreted, the system is reactivated to the original state and again can be inhibited by the administration of more gold. The reversibility of the process is therefore its most striking characteristic. In certain patients who showed no improvement, one may postulate that the process had become irreversible and could not be influenced by the action of gold. The patients showing slight improvement were those with the least improvement on subsequent administration of gold, suggesting that, in these patients, the process was tending to become irreversible. Thus a theory can be postulated as to the mechanism of rheumatoid arthritis, namely, that some mechanism is set in motion which can be inactivated by gold, which becomes reactivated when the gold is excreted and which is again inactivated on the subsequent administration of gold. That this mechanism is bacteriological presupposes that the gold exerts a bacteriostatic effect.[3] A more satisfying working hypothesis would be that the gold inhibits an enzyme system which becomes reactivated when the gold is excreted.

CONCLUSIONS

1. A group of 142 patients with rheumatoid arthritis treated with gold compounds has been studied over a period of three to four years.

2. The immediate response to treatment in this group corresponds to that reported elsewhere.

3. The long-term response to therapy is discussed. Eleven per cent showed no improvement, 75 per cent relapsed. Eighty per cent of those who relapsed and were treated again with gold improved again.

4. Rheumatoid arthritis with psoriasis responds less favorably to chrysotherapy than rheumatoid arthritis without psoriasis.

5. A theory for the pathogenesis of rheumatoid arthritis based on the response to gold is suggested.

6. It is believed that patients with rheumatoid arthritis treated with chrysotherapy who show improvement but no toxicity on the first course of therapy should be continued for an indefinite period on a maintenance dosage of gold.

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Review

The Diagnosis and Treatment of Diseases of the Anorectum*†

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HEMORRHOIDS represent varicose dilatations of one or more radicals of the hemorrhoidal plexus of veins. Good results are obtained by the injection treatment provided cases are selected. This form of therapy is indicated only in uncomplicated internal hemorrhoids. The high percentage of recurrence materially further limits its field of usefulness. We respect the fact that a hemorrhoidectomy properly performed is the procedure of choice. Unfortunately, various sequelae are encountered following the surgical removal of hemorrhoids, namely, hemorrhage, immediate and remote, severe pain, anal stenosis, residual infection, abscess formation, fissure and recurrence of the hemorrhoids themselves. The occurrence of such is due largely to the operative technic, lack of knowledge of the anatomy of this portion of the anorectum, the pathologic process itself, unnecessary trauma, failure to preserve adequate anal and perianal skin, inclusion of the sphincter muscle in the clamp and suture and inadequate after-care.

Because of the severe postoperative pain following hemorrhoidectomy, a technic was devised by us which has proved of value, not only toward the avoidance of pain, but also in the elimination of complications and sequelae.

Under low lumbar analgesia and with the patient in the jackknife position, a retracting speculum is introduced and the pile masses are drawn outside the anus in their respective quadrants. Additional hemostats are applied to the hemorrhoids to bring into view as much tissue as possible without undue tension. If external hemorrhoids are present, a small elliptic incision is made on each hemorrhoid in such a manner that it begins at a point just distal to the anorectal line, and is carried one-half inch beyond the tip of the external pile mass. The skin on either side of the hemorrhoid is elevated with fine forceps and the underlying tissue separated with small, blunt-tipped curved scissors.

The hemorrhoid is elevated and blunt dissection is begun at the apex where the two incisions are joined. The adjacent veins, which have been freed on either side are now drawn medially by an assistant and the operator continues with the blunt dissection on the surface of the external sphincter muscle. When the inner edge of this muscle is encountered, a small right-angle retractor is placed to draw the muscle

* Read before the Cambria County Medical Society, Johnstown, Pa. † From the Department of Proctology, Temple University Hospital, Philadelphia, Pa.

gently from the field of operation. A Smith hemorrhoidal clamp is placed on the internal hemorrhoidal mass in the longitudinal axis of the bowel and the mass cut away. A suture of No. 0 chromic catgut on a small curved needle is introduced one-quarter inch from the tip of the clamp and tied; the free end serves as an anchor. The base of the hemorrhoid is sutured beneath the clamp from side to side and continued to the opposite end of the hemorrhoidal base which lies immediately over the edge of the external sphincter muscle. The clamp is removed as well as the retractor and the muscle permitted to return to its usual location. It is unnecessary to approximate the cut edges resulting from the excision of external hemorrhoids, inasmuch as they fold together nicely as soon as the tonicity of the sphincter is restored.

Immediately on the patient's return to his room, the foot of the bed is elevated for six hours where a hypobaric (light) analgesic solution is used intraspinally. Liquids, a light soft diet and smoking are permitted. Compresses wrung out in hot boric acid solution are applied continuously. At night these may be supported by a hot water bottle. Morphine sulfate ¼ gr. or dilaudid gr. 1/20 is given only if necessary. The blood pressure in both arms is recorded every hour for six hours. The patient is permitted out of bed the following day. An aqueous solution of 1 per cent gentian violet is applied on a glass rod. Liquid petrolatum is given by mouth once daily for approximately one week. On the second postoperative day, an enema of warm saline or olive oil is administered through a No. 14 soft rubber catheter. Milk of magnesia (one-half to one ounce) is given by mouth daily thereafter. A house diet is prescribed and hot sitz baths thrice daily at a temperature of 110°F. and at a depth of six inches for five minutes are begun.

When discharged on the third or fourth postoperative day, the patient is advised to continue with the sitz baths and employ cotton tissue rather than toilet paper. The lubricated gloved finger is introduced five to seven days from the time of operation.

ABSCESSES

Anorectal abscesses demand surgical intervention. In the past it has been our custom simply to incise and drain unilateral and bilateral abscesses of the ischiorectal type. Later the fistula was corrected. In an effort to avoid multiple operations and protracted periods of hospitalization and convalescence, an attempt is now made to locate the primary or internal opening at the first sitting. In this type of abscess, the anorectal line is carefully examined, visibly, digitally and by means of a hook, for an ulcer, a crypt or a breech in the continuity of the skin or mucous membrane.

At the maximum point of fluctuation and beyond the outermost border of the external sphincter muscle, a stab wound is made into which a flexible metal probe is gently introduced toward the primary opening. The skin incision is carried to such a point that excision of the fistulous tract is at right angles to the fibers of the external sphincter muscle. The skin over the abscessed cavity is then widely excised to permit adequate drainage. A single strip of vaseline gauze may be placed in the fistulous wound for a period of twenty-four hours. It should be mentioned that for the novice this procedure is not to be recommended. It is better simply to incise and drain the abscess and later remove the fistula. We have performed this maneuver in selected cases in several hundred instances and have seldom encountered a recurrence. Operative wounds are rarely packed and never for more than forty-eight hours. Hot sitz baths are employed thrice daily.

BENIGN GROWTHS

Adenoma and papilloma of the rectum are not uncommon. In our series there have been twenty-nine cases in the young of which nineteen were boys and ten were girls. The ages ranged from fourteen months to eleven years. All lesions were located in the rectum or sigmoid colon. Twenty-one were visualized through the sigmoidoscope, and eight by roentgenologic studies employing opaque enemas and inflation of air. In the adult, these are usually observed during routine examinations but occasionally patients present themselves because of bleeding. With polypoid growths of large size pressure or obstructive symptoms are usual. When biopsy shows no signs of malignancy, destruction by fulguration may be instituted; especially is this true in children. Local excision may be employed in selected cases by a rectal approach. Polypoid lesions in the sigmoid require sigmoidotomy or transcolonic excision. Sessile processes which are usually detected by umbilication of the bowel are best removed by segmental resection.

MALIGNANCIES

Cancer of the rectum and sigmoid represents approximately 80 per cent of all intestinal malignancies. In the male, it is second only to that of the stomach. It is difficult to state accurately whether cancer is on the increase; certainly today this disease process is being observed with greater frequency. There are several reasons that may serve to explain this: first, improvements in diagnostic technic and the more widespread use of these methods; and second, patients are transitioned over the gaps of intermediary illnesses and therefore reach an age when cancer is more common.

A few years ago it was our privilege to review the literature on the incidence of malignancy of the anus, rectum and sigmoid in youth. One hundred twenty-three authentic cases were found below the age of twenty. Two cases that came under our observation were males. The first, four years and seven months old, had an adenocarcinoma of the rectum. The adenocarcinoma was resected and the patient is well six years following the operation. The second, three years and 8 months of age, had a reticulo-endothelial sarcoma of the rectum which was resected, but the patient succumbed seventeen months later. It seems expedient to state, therefore, that while the majority of cases of rectal and sigmoidal malignancy are encountered between the fortieth and sixtieth years, they may be observed at any age. In fact, we would rather say "there is no cancer age."

There are no pathogonomonic symptoms of rectal or sigmoidal malignancy, but there are complaints that are highly suggestive. The passage of blood, bright or dark red in color, occurring at, following or independent of the defecatory act, must be looked upon as a symptom of bowel malignancy until proved otherwise by various diagnostic means. Change in bowel habit, progressive constipation, alternate constipation and diarrhea, early morning diarrhea, incompleteness of evacuation, urgency and frequent desire for stool are suggestive of this dreaded malady.

One must be mindful that approximately 78 per cent of cancers involving the anus, rectum and sigmoid are within reach of the examining finger. Therefore, following a careful history, digital examination is of utmost importance. By proctosigmoidoscopy, with proper cleansing of the bowel, the entire rectum, lower and midsigmoid may be visualized in over 90 per cent of the cases examined. The presence of a fixed, nodular cauliflower-like growth involving the mucosal wall or a deep excavating ulcer with everted edges will serve to make the diagnosis. A biopsy may be made for con-

firmation, and in addition, will disclose the type and grade of tumor.

Where no lesion is demonstrated by careful digital and sigmoidoscopic examination, a roentgenologic study of the bowel, employing an opaque enema, is invaluable.

To cure cancer means early diagnosis and radical extirpation. It is definitely erroneous to assume that a malignant tumor of small size should be eradicated by a conservative operation or that one of large size should be removed by a very radical operation.

The radical one-stage abdominoperineal resection, advocated by Miles in 1907, is still considered by many the procedure par excellence. It permits wide removal of the gland bearing areas, offers a low recurrence rate and a low mortality. It presents one great disadvantage, namely, the establishment of an abdominal colostomy. For this reason alone, innumerable patients jeopardize their lives by refusing what radical surgery might offer. The ingenious procedure designed by Babcock in 1931 permits the same degree of wide excision of the malignant rectum and gland bearing areas with formation of a perineal anus in its normal location. By such, an abdominal colostomy is avoided. Approached through the abdomen and perineum (abdominoperineal proctosigmoidectomy), the cancerous bowel is dissected free and the vascularized sigmoid drawn down to the site of the normal anus. Prior to January 31, 1946, of 430 patients with cancer of the rectum or sigmoid, resection by various means was carried out in 345, a resectability rate of 88.0 per cent. Of this number "proctosigmoidectomy" was performed in 223 instances with fourteen deaths, a mortality of 6.2 per cent. With improvements and refinements in technic, preservation of the sphincter muscle has produced excellent results, in fact in our more recent cases the function may be described as practically that of the normal. The vast majority of our patients are out of bed on the fifth or sixth day, discharged on the eleventh and return to work six to ten weeks following resection.

PROLAPSE

Except for those cases which present extensive procidentia and prolapse, the condition is seldom recognized, yet it is one of the most frequent entities to be encountered. Any factor, whether anatomic, mechanical or inflammatory, that tends to diminish the normal fascial, muscular or peritoneal supports of the rectum, thereby increasing the motility, is conducive to prolapse and/or procidentia. To one accustomed to the use of the proctosigmoidoscope with the patient in the inverted or knee-shoulder position, varying degrees of mucosal prolapse are easily discernible. Only too frequently these patients offer a history of chronic constipation, an indeterminate type of pressure, a fullness or weight in the pelvis, and incompleteness on evacuation of the bowel. Careful examination discloses complete absence of the normal mucosal pattern, and partial or complete obliteration of the valves of Houston. Marked redundancy and reduplication of the rectal mucosa will be noted by digital examination and through the sigmoidoscope. Not infrequently the condition is associated with redundant sigmoid as evidenced by roentgenographic study following an opaque enema.

In children, prolapse is amenable to injections of quinine and urea hydrochloride or phenol in oil given in ¼ cc. dosage circumferentially at graduated levels. In adults, a modification of the procedure, advocated by Murietta in 1938, is ideal. The patient is placed in the inverted position under sacrocaudal or lumbar analgesia, and the prolapse of the anterior wall drawn taut longitudinally and clamped. The prolapse is excised and a running mattress of fine chromic catgut introduced beneath

the clamp. The suture line is inverted by a second catgut stitch. The posterior wall is drawn taut in a transverse fashion. Anchor sutures are placed at the extreme ends and as the prolapsed bowel is excised, clamps are applied to the cut edges of the mucosa. A running mattress of fine chromic is introduced and the resultant line of suture inverted by a second layer. Over 1,000 patients have been operated upon by this method with gratifying results. In this series two cases of hemorrhage and three of stenosis were encountered.

For procidentia, the surgical approach should be abdominal embodying fixation, obliteration and occasionally plication.

CHRONIC ULCERATIVE COLITIS

Chronic ulcerative proctosigmoiditis, described by some as thrombo-ulcerative proctosigmoiditis, is a condition frequently observed. Characterized pathologically by typical changes in the intestinal wall and clinically by its progressive course, the passage of frequent bloody, mucopurulent discharges, tenesmus, abdominal pain, and general lassitude, it is not difficult of diagnosis. One should be mindful that 95 per cent of these cases have their origin in the rectum or lower sigmoid. This, itself, gives evidence of the necessity for proctosigmoidoscopy in routine examination.

Early in the disease, the mucosa exhibits a rather diffuse hyperemia. As the process continues, edema and pitting of the mucosa is apparent. Minute yellowish abscesses may be seen beneath the mucosal layer, which upon rupture form ulcers which give a moth-eaten appearance to the already granular lining of the membrane. In some cases an ironed-out or rounded appearance of the valve edges is discernible. At a later stage, confluence of these petechial ulcerations form large ragged areas. Fever of the septic type is not uncommon, especially during the acute stage, or in exacerbations of the chronic. Ordinarily the blood count discloses a secondary anemia and a mild leucocytosis. In all these cases it is highly expedient to study the case thoroughly in order to rule out a specific influence. Smears are made by scraping the rectal mucosa and vaccines prepared when pathogenic organisms are found. An opaque enema is administered for the purpose of determining the upper extent of the disease process. In febrile cases, bed rest is imperative. Factors influencing the physical and mental status of the individual are corrected. In fulminating cases, parenteral feeding is employed, otherwise a diet that is of low residue, bland, high in calories, vitamins and proteins, yet low in starch and sugar is prescribed. We have found that frequent small blood transfusions have proved most efficacious. Locally, where the process is confined to the rectum and lower sigmoid, gentian violet, 2 per cent aqueous solution through the sigmoidoscope with insufflation of sulfanilamide has proved advantageous. Retention enemas of olive oil and cod liver oil may be judiciously used. For diarrhea, kaomagma, kaopectate by rectum and by mouth is usually satisfactory. A mixture of bismuth subcarbonate ℥i in warm olive oil ℥iv by rectum three or four times daily is beneficial.

Vitamin therapy has proven to play a most important part in the melioration of this condition. Vitamin A, 100,000 units intramuscularily, vitamin B complex, containing thiamin chloride 20 mg., nicotinamide 150 mg., riboflavin mg. 4, pantothenic acid mg. 5, pyrodoxine mg. 10, twice daily. Sodium ascorbate 500 mg. daily is administered intravenously. This is continued during the period of hospitalization. We have observed beneficial results with neoprontosil, gr. 5, every six hours for ten days. Sulfathalidine has been employed in forty-seven cases; there were four reactions; improvement was observed

in thirty-five patients; twelve showed no benefit.

PRURITUS ANI

Pruritus ani is a syndrome embodying an alteration in the anal and perianal skin, due to irritation in the peripheral nerve endings, caused by some local or systemic disease. The chief symptom is itching, which is characterized by its chronicity, rebelliousness to treatment and tendency to recurrence.

So long as there is no one specific cause of pruritus, just so long will there be no specific treatment. Much has been written and suggested for this distressing malady, and while the treatments have been worrisome and frequently unsatisfactory, the chief purpose in following any procedure is to allay the distress while attempting to seek the cause. The examination should be thorough and untiring, using every available means to find some influencing factor. Should any anorectal disorder be discovered, it must be corrected. Invariably, where such a pathological condition exists, its removal will result in definite improvement. Cleanliness is essential and may be accomplished by washing the anus and surrounding areas with warm water and castile soap twice daily and after defecation. Absorbent cotton is preferable to any toilet paper now in use. Irritations from tight clothing, tending to rub the anal skin, should be avoided.

Importance of the dietary régime should not be underestimated; not only are certain foods irritating of themselves, but the manner in which even bland foods are prepared and seasoned may render them unsuitable. Green vegetables, especially spinach, peas and carrots, are permitted, as well as potatoes, milk, cereals and fruits, both fresh and stewed. Fowl and moderate amounts of unseasoned red meat may be taken. Water should be consumed liberally. Such foods as oatmeal, salt fish, oysters, clams, crabs, lobsters, cheese, pickles and cucumbers are interdicted. Excessive eating, the use of condiments, and overindulgence in alcohol are to be avoided, as well as a superabundance of seasoning.

Inquiry as to the general health and habits of the individual should be made. Fresh air, sunshine and rest are advocated for an impaired general condition. Tonics of iron, phosphorus, arsenic and cod liver oil may aid generally in improving the health.

It has been shown that nervous irritability in these cases should not be minimized, and for this potassium bromide, 5 to 10 gr., or phenobarbital, either the sodium salt, ¼ gr., or the elixir, ½ to 1 dr. is given every three hours for a few days.

Insomnia may be relieved by the use of one of the barbiturates, as luminal, 1 to 2 gr., nembutal, 3 gr., or bromide, 10 to 20 gr., using either the sodium or strontium salt. The opiates are interdicted.

Sluggish intestinal evacuations may be corrected by the use of one of the following given once or twice daily as necessary: Cascara sagrada, ½ to 1 dr., magnesium sulfate, ½ to 2 dr., liquid petrolatum, ½ to 1 ounce; or enemas of plain hot water, salt water, or warm olive oil. As an intestinal antiseptic, the sulfocarbolate of zinc, 5 gr. every two hours, is advocated after proper bowel function has been restored.

Associated anorectal disorders, such as hemorrhoids, fistulas, cryptitis, papillitis, condylomas, skin tags, proctitis, etc., should be corrected. Helminths, as pin or threadworms (oxyuris vermicularis) may be destroyed by use of santonin, 1 to 3 gr., or calomel, 2 gr. given for three successive nights. Where fungi have been demonstrated, the administration of potassium iodide, saturated solution, beginning with 20 drops thrice daily and increasing one drop until the symptoms of iodism appear, is recommended. Thereafter, the dosage is

decreased slightly and continued for several weeks. Many patients improve upon reaching the saturation point and remain symptomatically free for varying periods of time. Whitfield's ointment and Deek's ointment (salicylic acid, 4 per cent, mercury salicylate, 4 per cent, oil of eucalyptus, bismuth subnitrate, 10 per cent, in a mixture of equal parts of lanolin and petrolatum) are of value. Rectal irrigations of lime water, quinine bisulfate, 1:2000, infusion of quassia, 5 per cent; saline solution (1 ounce to 1 pint of water), acetic acid, ¼ to 1 per cent solution, and turpentine or benzine may be instituted.

Dermatologic conditions, such as eczema marginatum and tinea trichophytina, may be eradicated by salicylic acid, 10 to 15 gr., to 1 ounce of petrolatum; crude coal tar, ½ dr. to 1 ounce, liquor detergens, ½ dram to 1 ounce; or the following:

R
Iodi ..... gr. xx
Potassi iodidi ..... gr. xl
Acidi salicylici ..... gr. xlv
Acidi borici ..... ʒiss
Alcoholis ..... ʒiii
(50% ..... q.s.fl.)
M. et ft. solutio.
Sig.—Apply locally and allow to dry.

In mild pruritus, the following may be used:

R
Phenolis ..... gr. x
Lotio calaminae, q.s.fl ..... ʒiii

R
Acetanilidi ..... ʒi
Petrolati ..... q.s. ʒi
M. et ft. unguentum.

In some cases, citrine or chloroform ointment will allay the itching. If the area is moist, dusting powders, as zinc stearate or calomel, may be used. The following is recommended:

R
Dithymol-diiodidi ..... ʒi
Bismuthi subcarbonatis ..... ʒiii
M. et ft. pulv.

The skin should be washed with warm water and castile soap and dried before the powder is applied. If the skin is thick and leathery, mercury, phenol, 1 to 5 per cent in lotion or ointment form and silver nitrate, 1 to 15 per cent are stimulating. Potassium permanganate, saturated solution (29½ gr. in 1 ounce water), may be painted over the surface daily. Liquor potassae, solution of mercuric chloride or a 10 per cent nitrate of mercury ointment have proved of value. If the skin is acutely inflamed, calomel and lime water may be applied:

R
Hydrarg. Chlor. mitis ..... gr. xvi
Liquor calcis ..... q.s. ʒiv

Cracks, fissures, and excoriations may be treated by topical applications, using a glass rod or stick, of (1) phenol, 90 per cent solution, neutralized by tincture of benzoin; (2) silver nitrate, 10 to 20 per cent solution or stick, neutralized by tincture of iodine; (3) silver nitrate, 50 per cent solution, used alternately with citrine ointment; (4) pure ichthyol; or the following:

R
Phenolis ..... gr. xx
Acidi salicylici ..... ʒi
Camphorae ..... gr. v
Glycerini ..... q.s.fl. ʒi
M. et ft. solutio.
Sig.—Apply locally.

Following the use of the foregoing prescription, when excoriations are healed, tincture benzoin may be applied, or the following:

R
Balsami peruciani
Olei ricini ..... aa fl. ʒi

In all cases, it is advisable to make a smear of the anal and perianal skin preferably by means of a cellophane glass rod. Culture of the organisms and subsequent injections may effect a cure.

Recently decided benefit has been obtained for patients with pruritus by regulating the hydrogen ion concentration of the surface of the rectal mucosa. In pruritus the

concentration is usually above 7.5. After the administration of an acid-ash diet and a capsule of glutamic acid, hydrochloride gr. 5 and pepsin gr. 1 with each meal, the hydrogen ion concentration is lowered and the symptoms abate in the majority of the cases. In the more refractory patients, it has been found advantageous to employ a nightly retention enema of 2 ounces of lactic acid (2½ per cent solution) in a pint of water. With this form of therapy, other methods of treatment, particularly those contributing to cleanliness, are combined.

Injection Methods. As is well known, alcohol possesses a destructive effect on the nerve structures and for this reason has been employed in the treatment of pruritus ani. Stone advocated the subcutaneous injection of 95 per cent grain alcohol to destroy the terminal sensory filaments that supply the diseased area. In a few hundred instances we have employed varying strengths and amounts of alcohol and although many sequelae have been encountered such as abscess, necessitating free incision and drainage on one or more occasions, as well as a protracted convalescence, our conclusions are that it is an excellent means toward the eradication of this distressing syndrome. Under sacrocaudal or sodium pentothal anesthesia, the parts are thoroughly prepared, and 40 to 60 cc. of alcohol 47.5 per cent are injected subcutaneously around the sphincter muscle. Other preparations and solutions such as hydrochloric acid, benacol, distilled water, quinine and urea hydrochloric and anucaine, may be employed.

The hypothesis of Besredka as applied to the pruritic syndrome entails the taking of cultures from the anal and perianal region of patients suffering from pruritus. The débris or scrapings before and after sterilization are planted in hormone broth and incubated at 37.5°c. for seventy-two hours. After identification of the organisms, the culture is passed through the Berkefeld filter and the antigen completed by the addition of 3 drops of tricresol 0.1 per cent solution as a preservative. The prepared autogenous vaccine is injected intradermally and subcutaneously into the pruritic area after cleansing of the surface with alcohol. Initially 5 to 6 minims is introduced and the dose gradually increased until 16 minims (1 cc.) are given. Injections are given every third day. Two to four areas are treated at each sitting. The writers instituted this treatment a few years ago as previously reported.

The value of surgery in the treatment of pruritus ani is indeed problematic. Certainly it should be resorted to only after co-existing disorders have been corrected and at least one or even two forms of the injection treatment have been given a fair trial. The operative means of combatting pruritus ani confines itself to (1) the removal of the diseased skin; (2) severance of the sensory nerve filament supplying that skin; and (3) division of the peripheral nerves following their identification by means of a faradic current.

PILONIDAL CYSTS

Pilonidal cysts and sinuses are encountered with comparative frequency. Pain and discomfort of varying degree, swellings and mucopurulent discharge with incision and drainage on one or more occasions, are usually cited by the patient. Examination discloses one or more openings in the midline or adjacent skin overlying the sacrococcygeal region. An inflammatory process presenting increased heat, swelling, tenderness, induration redness and fluctuation, with pus discharging from the opening and perhaps a tuft of hair extending therefrom, leaves little doubt as to the diagnosis.

The treatment is distinctly a surgical one and consists of the removal of the cyst and all tributary tracts. The relative merit of

closing or permitting the resultant wound to heal and fill in by granulation is and probably always will be a moot question. Over the ten-year period ending 1938, a series of 414 operative cases were studied in the proctologic clinics of the Graduate and Temple University hospitals. Conclusions drawn from this survey have established rather definite criteria for both the open and the closed methods.

Pilonidal cysts and sinuses presenting acute abscess formation, and/or multiple tracts and openings and/or definite involvement of the sacrum or coccyx, are best excised in their entirety and left open to granulate in from the bottom. Recurrent cases fall in this category also. Conversely, pilonidal cysts and sinuses of small or moderate size presenting congenital midline openings, and devoid of an acute inflammatory process with abscess formation may be sutured. In the latter, as in all cases, all existing pathological conditions must be removed, hemostasis complete and all dead spaces obliterated. For closure, interrupted sutures of No. 32 alloy steel wire placed in tier formation are introduced until the skin is reached. The skin itself is not approximated. From 1938 until the present, 154 private patients have been treated by the above criteria. All have been followed carefully. In seventy of the 154 cases, the average period of hospitalization was three and three-fourths days; the average period from the date of operation until complete healing was noted as thirty-nine days or approximately five and one-half weeks.

LYMPHOGRANULOMA

Probably the most fascinating disease entity drawn to our attention during the past decade and a half is lymphogranuloma inguinal or lymphopathia venereum. To us, it is of special interest by virtue of the fact that inflammatory stricture of the rectum, and esthiomene of the anoperineal and anovulvar region, are most frequently due to the filterable virus of lymphogranuloma venereum. Stricture of the rectum is an organic narrowing of the lumen of the bowel by fibrous tissue involving the mucous membrane, submucosa and muscular coat. It is characterized by progressive constipation, tenesmus and mucopurulent discharge. Rectal manifestations are more common in the female because of the distribution of the lymphatic network. The condition is more frequent between the ages of seventeen to forty, or the period of greatest sexual activity. Also there is a marked preference for the colored race. In our series were 1,124 cases, 729 of which were negroes.

It should be borne in mind that the inflammatory process may attack any layer of the rectum or the tissues outside its wall. If from within, the irritation results in erosion of the mucous membrane, upon which infection is superimposed. With continuation of the etiologic irritant, the inflammatory process becomes subacute and finally chronic in nature, so that the various layers of the rectum and tissues outside its wall are gradually involved by continuity and contiguity of structure. As a result of this chronic inflammation, much young fibroblastic tissue is deposited in the submucosa as well as in the other coats, which gradually leads to thickening of the visceral wall. This in itself tends to encroach on the lumen of the rectum. By subsequent contraction of the maturing fibroblastic tissue this thickening becomes markedly increased, so that there eventually results a firm, inelastic, permanent narrowing, to which the term stricture is applied.

On the other hand, if the initial focus is outside the rectum, as the writer believes is more frequently the case, the extramural network of lymphatics becomes invaded. As the inflammatory process gradually becomes chronic, the mural tributaries, i.e., the intermural and intramural groups, are

invaded by extension. As a result of the inflammatory process, fibrous tissue is deposited in the various layers of the rectum so that thickening occurs which brings about narrowing of its lumen. As the process continues and additional fibroblastic tissue is deposited, subsequent contraction ensues, so that finally an organic stricture is formed. Erosions of the mucous membrane are noted, followed by ulcerations, and the surrounding mucosa appears altered and somewhat lusterless. To the touch, the involved area is thick and firm, while later it feels leathery with loss of elasticity and distensibility. It is more or less irregular, markedly thickened, and the mucous membrane is found to be adherent to the tissue beneath. In the deeper layers of the stricture, fibrous tissue is seen involving all the coats of the rectum, although the greatest amount of involvement is in the submucosa. Fistulous tracts may be found passing through the perirectal tissues to adjacent structures, as the bladder, urethra, vagina or through the skin. Ulceration is usually marked and occurs early. The discharge is frequently abundant, mucopurulent and often sanguineous. Ulceration rarely exists at the level of the stricture except in the tubular variety, which is seen routinely through the stricturoscope and at autopsy.

A history of constant soiling by feces, blood and pus is suggestive of an inflammatory stricture, especially when cited by a colored female between the ages of twenty and forty. Although the diagnosis by inspection is not absolute, it offers to the careful observer a very good idea of the pathological condition present. Not infrequently, the region about the anus is moist and glued together by the thick mucopurulent discharge. Upon separation of the buttocks, fecal matter mixed with blood and pus may be seen seeping through the anal orifice. Hypertrophied skin tags, condylomas of various sizes, and one or more fistulous openings are not uncommon. Since approximately all inflammatory strictures of the rectum are within reach of the finger, the diagnosis should not be difficult. As the gloved finger is inserted into the anal canal, some degree of muscular relaxation will be noted in long-standing cases, due to fatigue of the external sphincter, yet gentleness should attend this procedure, since pain and discomfort are not unusual. As the finger is advanced the stricture will be felt as a firm inelastic narrowing, usually involving the entire circumference of the rectum. If the lumen of the stricture is of sufficient size to admit the tip of the index finger, the finger usually can be passed to its entire length. However, such introduction should be attended by great care, since forcible insertion not only causes pain but is dangerous, because the diseased tissue is so friable that hemorrhage and perforation may ensue. Through an ordinary proctoscope the stricture, or, in the case of the tubular variety, the lower border of the stricture, is noted by its pale, leathery, and thickened appearance. In each case, especially if the stricture is located in the sigmoid or at a high level in the rectum, roentgenograms should be taken after an opaque enema.

In 1925, Frei, of Berlin, introduced a cutaneous test for this disease which has proved of distinct diagnostic value in inguinal adenopathies and anorectal syndromes. More recently we have employed the chick embryo antigen (Lygranum) and have found it more specific. Use is made of yolk sacs harnessed from chick embryos moribund or recently dead from infection with the agent of lymphogranuloma venereum and containing the agent in high concentration free from contamination with other micro-organisms or viruses. The technic for testing patients diagnostically is the same for both antigen and antigen control. After preparing the skin of the fore-

arm with alcohol, 0.1 cc. of each material is inoculated intradermally into the forearm and the reaction is read at forty-eight and seventy-two hours by measuring the diameter of the resulting papules. A papule 6 by 6 mm. or greater indicates a positive reaction providing the papule produced by the antigen control is 5 by 5 or smaller. Of twenty-four intradermal tests, twenty-two positive reactions were observed which were confirmed by clinical and histopathologic study.

In every case effort must be made to ascertain the cause and any influencing factor in order that treatment may be instituted accordingly. For instance, if syphilis co-exists, proper antiluetic treatment should be given even though it has no effect on the fibrotic stricture; if the patient is tuberculous, measures should be directed thereto. Attempt should be made to build up the constitution of the patient, since there are usually varying degrees of weakness and loss of weight. The diet should be nutritious and composed of foods which leave little residue. Ordinarily a low residue diet in four feedings is composed of protein 120 Gm., carbohydrates 400 Gm. and fats 50 Gm., supplemented with amino acids 15 per cent solution. Instillations of ichthyol, 2½ to 5 dr. (10 to 20 cc.) of a 25 per cent aqueous solution twice daily are soothing to the mucous membrane and will assist in diminishing tenesmus.

Perineal excision preceded by a permanent colostomy is applicable for all variations of stricture of the rectum. The procedure recommends itself because it is not so formidable as other types of excision, and irrigations through the distal colostomy loop may be instituted. Fifty-one such operations (Lockhart-Mummery technic) have been performed by one of us (H. E. B.) with one death (1.9 per cent), twenty-four of which were previously reported. A number of abdominoperineal extirpation (Miles technic) have likewise been done with one death. Negroes, are loath to accept an abdominal stoma because of their age group and their type of occupation so that in their race, too, we have found it desirable to perform an abdominoperineal resection (proctosigmoidectomy) without colostomy and with preservation of the sphincter musculature. This technic has been employed in nineteen patients; and while convalescent period in some instances was quite protracted, there were no deaths. Of course, in the presence of pararectal abscesses and fistulas with free suppuration, incision and drainage is indicated followed later preferably by a two-stage interval resection. Preliminary *x*-ray therapy was used in a small series of cases for the purpose of demonstrating the size of infection; the results were highly satisfactory.

ANAL STENOSIS

During the past few years many cases of anal stenosis have been observed usually as the result of removing "too much skin" at the time of operation. In our operations for cancer "proctosigmoidectomy" where the sigmoid is drawn through the anal orifice, we have experienced more than an occasional case of narrowing at the junction, so that an ample opportunity to employ various technics for correction has been afforded. The method devised by Martin of Detroit has proved of special value and has been utilized in over 250 cases without a single failure. The technic is simple and consists of mobilizing a small portion of the mucous membrane immediately above the stenotic area and preferably in the posterior phase. A slit through the stenosis in this site is made following which the mobilized mucous membrane is tacked to the marginal wound with two or three interrupted sutures of chromic catgut. Subsequent dilatation has at no time been necessary.

Seminar on Antibiotics

Penicillin Aerosol and Negative Pressure in the Treatment of Sinusitis*

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THE physiologic basis for the use of penicillin aerosol and negative pressure in sinusitis may be stated as follows: A negative pressure of approximately 60 mm. Hg is intermittently produced in the sinuses during the inhalation of a fine mist of penicillin. Air withdrawn from the sinuses during the suction cycle is replaced by penicillin aerosol when the pressure in the nose becomes positive. Aeration and drainage of the paranasal cavities, with deposition of penicillin on the mucous membrane, follows this procedure unless the orifices to the sinuses are completely obstructed.

In earlier studies on nasal inhalation of penicillin aerosol beneficial results were at times observed in patients with sinus infections.[1–4] More favorable reports from inhalation of penicillin through the nose at atmospheric pressure have appeared, notably that of Vermilye.[5] Although ventilation of the sinuses takes place in some instances during normal breathing by the slight negative pressure in inspiration producing a venturi effect in the orifices that lead to the paranasal sinuses, a more efficient ventilation of these cavities was achieved by creating a negative pressure of 50 to 70 mm. Hg in the nasal passages with immediate replacement of the air withdrawn by penicillin aerosol.[6] The apparatus devised for this purpose and a report of its clinical effect in acute and chronic sinusitis indicated that this procedure had therapeutic value.[6,7]

The antibiotic effect of penicillin depends on the entrance of the nebulin of this drug in sufficient concentration to result in bacteriostasis and on the presence of penicillin sensitive organisms in the sinuses. Previous experience with oral inhalation of penicillin in bronchiectasis and other bronchopulmonary infections has revealed the specific value of aerosol therapy in patients with infections caused by pneumococci, hemolytic streptococci and Staphylococcus aureus.[1,2,5,7,8,9] At times improvement has been obtained in patients with bronchial infection due to Streptococcus viridans. Penicillin is known to be effective locally in high dilutions and has the advantage over chemotherapeutic sulfonamide aerosols previously used[10–14] in that this newer antibiotic is not inactivated by purulent exudates or para-aminobenzoic acid.

In cases of mixed infection, however, a favorable response to penicillin therapy

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† Representing Research Division, Bureau of Medicine and Surgery, U. S. Navy; and Medical Division, Chemical Warfare Service, U. S. Army.

frequently does not take place. This may be due to the pathogenic character of the organism, such as the colon bacillus, or it may be due to gram-negative bacteria which produce an enzyme that nullifies the bacteriostatic effect of penicillin, as Abraham and Chain[15] first pointed out. The enzymatic nature of "penicillinase" has been substantiated by Woodruff and Foster.[16] Meleney[17] has also recently demonstrated that para-chloralphenol is effective against gram-negative organisms and that when it is used in surgical mixed infections results in a marked increase in the clinical effectiveness of penicillin. In the first report on inhalation of penicillin aerosol in bronchopulmonary disease[1] it was noted that the gram-positive organisms were generally absent in the sputum culture after effective therapy and that gram-negative organisms were then found on culture, especially Bacillus aerogenes, pyocyaneous, proteus and coliform organisms. Our belief was that these organisms that appeared subsequent to treatment grew out more easily following the disappearance of gram-positive bacteria. Although gram-negative bacteria may not in themselves be pathogenic, the growth of these bacteria may at times prevent the beneficial activity of penicillin by the "penicillinase" mechanism referred to above. Recent experience in our clinic has tended to confirm this point of view.

In a series of seventy-five patients with bronchiectasis treated by Olsen[18] 50 per cent were found to be resistant to this drug and 50 per cent showed marked improvement. In eleven patients whose response has been poor, the addition of streptomycin aerosol resulted in the disappearance of the gram-negative organisms and conspicuous reduction in the volume and purulent character of the sputum with corresponding clinical benefit. The striking cures obtained by Segal[19] in pneumococcus lobar pneumonia reveal the effectiveness of penicillin aerosol in a single infection with a sensitive organism. Although mixed infections, such as are found in lung abscess as well as chronic pulmonary disease, are at times markedly benefited by penicillin aerosol,[1,19] the newer findings on the significance of gram-negative organisms has encouraged the investigation of streptomycin aerosol as well as para-chloralphenol and sulfacetamide to be used in combination with penicillin. In requesting sputum cultures it seems important now to ask for the list of organisms present, especially the occurrence of gram-negative organisms. The bacteriology of all the micro-organisms found in a sputum would require a large amount of careful work and may not always be feasible. However, the presence of organisms which have a gram-negative stain should be noted in the report, even if the exact nature of the bacteria may not be completely worked out.

The antibiotic effect of penicillin nebulin introduced in the sinuses cannot be entirely separated from the effect of negative pressure itself, in that better aeration and drainage might be of therapeutic value in itself. The value of reduced atmospheric pressure in a low pressure chamber was reported by Andrews, Roth and Ivy[20] in the treatment of paranasal sinusitis. However, the employment of negative pressure itself in the sinuses without an antibiotic might result in secretions entering uninfected sinuses without the protection of a drug that will act to inhibit bacterial growth. In the cases previously reported as well as the present series no instance of an infection of an uninfected sinus cavity has been observed when penicillin aerosol was used in conjunction with intermittent negative pressure.

METHODS

The apparatus originally described[6] included a nebulizer with a rebreathing bag and cone-shaped glass nosepieces for nasal

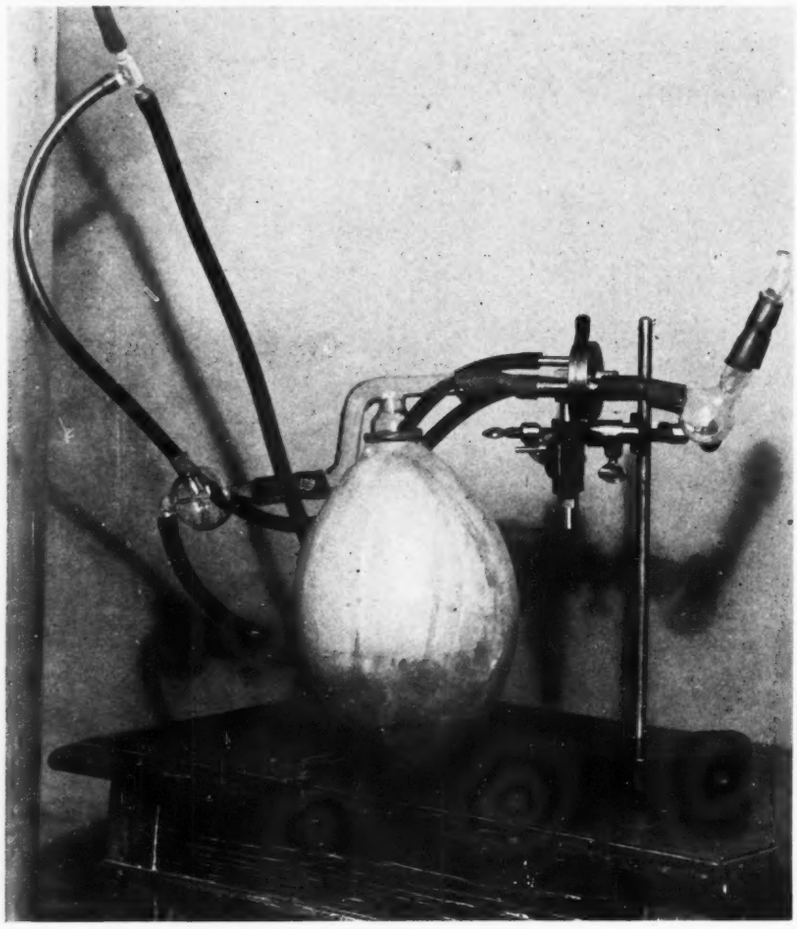

FIG. 1. *Apparatus for penicillin aerosol with rebreathing and negative pressure.*

inhalation of penicillin. A glass venturi tube inserted in the rubber tubing from the oxygen cylinder was used for the production of positive pressure by oxygen flowing through the distal end and for negative pressure through the side arm. A specially constructed valve connected the nebulizer to positive pressure when its handle was upright and to negative pressure when it was turned downward. The patient begins by taking three breaths of penicillin mist; the handle of the sinus valve is turned downward and he is then instructed to swallow. In this position the patient is connected with the side arm of the venturi and a negative pressure of 50 or 60 or more mm. Hg is produced, depending upon the flow of oxygen from the regulator. When the nasopharynx is closed a suction effect within the nasal passages is experienced by the patient and the nose is drawn inward; the handle of the valve is turned upward, oxygen passes through the nebulizer and inhalation of penicillin aerosol takes place again for three breaths.* (Fig. 1.)

In a more recently developed apparatus negative pressure and a slight positive pressure is used. (Fig. 2.)† Penicillin is produced during the phase of positive pressure and enters the nose while the patient breaths partly through the nose and partly through the mouth. The rebreathing bag is eliminated. After three breaths the valve is turned downward, the patient is instructed

* The apparatus is made by Mr. F. F. Anderson, 4652 Spuyten Duyvil Parkway, Bronx, 63, New York.

† This apparatus is manufactured by the Oxygen Equipment Mfg. Co., 405 E. 62nd Street, New York City.

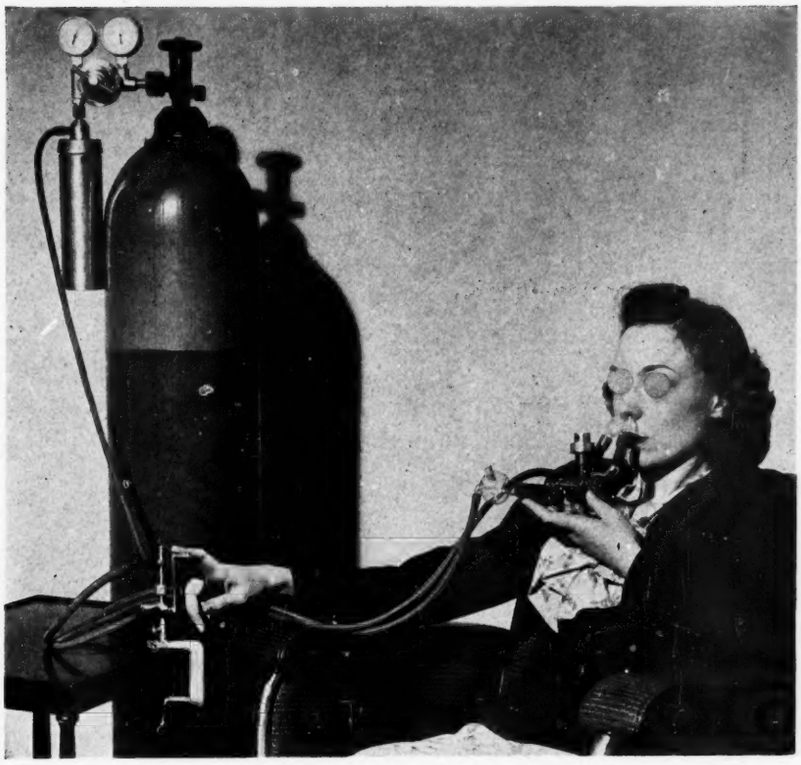

FIG. 2. *Apparatus for penicillin aerosol without rebreathing and negative and positive pressure.*

to swallow and as soon as the experience of suction is felt, the valve handle is turned upward and the patient is then told to exhale through his nose. An expiratory valve which opens at a pressure of 20 mm. Hg is set in a glass trap designed for the collection of secretions that may be sucked from the nasal passages and sinuses. When the patient exhales through his nose a moderate positive pressure is maintained by oxygen which carries a relatively dense mist of penicillin aerosol. In the positive phase the patient does not swallow and pressure on the Eustachian tube is thus everted. Since higher pressures than 20 mm. Hg were occasionally uncomfortable, the valve has been set to give this pressure. Penicillin may then be introduced into the sinuses when the negative phase is terminated by atmospheric pressure and also during the positive cycle. After the patient has exhaled through the nose three breaths are again taken in order to fill the nasal passage with penicillin mist and the procedure is repeated.

The use of penicillin aerosol is at times followed by soreness and redness of the tongue or by a black coating on the tongue. It was previously found from studies on the oral administration of penicillin in water[21] that the tongue not infrequently showed the characteristic changes mentioned above. This took place to a lesser extent when the mouth was washed immediately after ingestion of penicillin solution. Evidence is not at hand to explain the precise cause of sensitiveness of the tongue to penicillin, either in solution or in aerosol form, but it seems to be definitely related to the local effect of penicillin.

Elimination of the larger sized particles in penicillin aerosol was tried to avoid this complication by connecting a baffle to the Vaponefrin nebulizer on which larger particles would be precipitated, and then washed back into the nebulizer and re-used,

and by the construction of a nebulizer in which small particles were more consistently produced. In addition, it was found more comfortable for the patient who inhaled penicillin orally to humidify the aerosol by placing hot water in the rebreathing bag and by having the rubber bag itself placed in a container of hot or boiling water. In the sinusitis apparatus the technic has been changed recently to include the instillation of hot water into the glass trap connected to the nose pieces. Although the nasal mucous membrane itself generally shows no signs of irritation with the inhalation of 50,000 units of calcium or crystalline penicillin per cc., exhalation of the mist over the tongue without the precautions mentioned above has at times resulted in either reddening of the tongue or the development of a black deposit on its surface. Studies are in progress to determine the effect of the two modifications mentioned above: (1) the use of a small particle size aerosol and (2) humidification of the aerosol prior to entering the nose and mouth. When the rebreathing bag is punctured by a hole ¼ inch in diameter, the excess oxygen and aerosol is eliminated. In the apparatus without the rebreathing bag the aerosol is exhaled through the nose. The cause of the red or black tongue does not appear to be related to the concentration of the aerosol since it develops when penicillin is swallowed in solution with a concentration of 500 units per cc. Whether this transient complication will occur with crystalline penicillin remains to be seen; if it is due to a change in bacterial flora, the main remedy to avert it may be rinsing the mouth with water after each inhalation. A marked variation in individual susceptibility has been manifested since some patients have no such reaction after months of therapy and others will develop it in three days.

In cases of chronic sinusitis treated in the hospital, or at home, the customary procedure has been the nasal inhalation of 50,000 units of penicillin aerosol in 1 cc. of saline with negative pressure four times a day. In a few cases penicillin has been given systemically before retiring, either orally or by injection. In some patients with acute sinusitis, or with an acute exacerbation of a chronic sinusitis, a single treatment a day has been employed for a period of three days to two weeks. The indications for the frequency and length of treatment cannot be concisely outlined at this time, but in general it may be said that patients with chronic disease are more apt to require three or four treatments a day.

EXPERIMENTAL RESULTS

Experiments were conducted to determine the pressures in the nasal passages and in the antrum during the negative phase of the treatment. Two patients who had persistent oral-antral fistulas following extraction of upper molar teeth were used as subjects.* A catheter attached to a mercury manometer was passed from the mouth into the antrum. Pressure readings for the nasal passages were obtained by connecting a mercury manometer to the glass nose piece. Pressure readings from a typical experiment were as follows:

Oxygen Flow Liters Per Minute	Pressures in Mm. Hg below Atmospheric	
	In Nasal Passages	In Antrum
3	22	20
4	40	36
5	60	52
6	90	64
7	148	65
8	156	69

The pressures within the antrum follow closely the pressures within the nasal pas-

* These volunteers were obtained through the cooperation of Dr. Morris Hickey of the School of Dentistry.

ages at oxygen flows of 5 liters per minute or below. At higher rates of flow negative pressure within the antrum reach a plateau and then do not materially increase. When the negative pressure in the nasal passages is excessively high the mucous membrane surrounding the ostium may be sucked in and occlude the opening. In some cases when the suction in the nasal passages was released and the pressure in the nasal passages became atmospheric, a negative pressure of approximately 60 mm. Hg would persist in the antrum, dropping suddenly after ten or fifteen seconds. This would confirm the view that the ostium may be temporarily occluded by too high negative pressure.

The subjects with oral-antral fistulas were also used in experiments conducted to determine the amount of penicillin reaching the antrum during the treatment. Following a treatment with 50,000 units of penicillin aerosol administered with the alternating pressure apparatus, 7.5 cc. normal saline was introduced into the antrum through the catheter and withdrawn a few minutes later. Amounts of penicillin recovered varied from traces to 70 units. These figures were found to represent only a portion of the penicillin present, the remainder being absorbed or clinging to the mucous membrane. Thus, when 5,000 units of penicillin in 5 cc. saline were introduced through the catheter only 376 units could be recovered twenty minutes later, approximately 7 per cent of the amount instilled.

A second group of experiments was carried out to determine whether penicillin entered the antrum only in the form of an aerosol or whether the mist was deposited on the walls of the nasal cavity, including the external opening of the ostium, and sucked into the sinus in the form of a liquid during the phase following the release of suction.

A subject was instructed to take three inhalations of an aerosol containing 50,000 units of calcium penicillin in 1 cc. normal saline. The nosepieces were removed and he inhaled three times through his nose and out his mouth; the nose pieces were replaced and suction was applied. The degree of negative pressure obtained in the antrum was measured by attaching the rubber catheter to a mercury manometer, and averaged 80 mm. Hg. The nose pieces were then removed until the manometer reached the zero mark and the cycle repeated sixty times. At the termination of this procedure, which required about thirty minutes for completion, the antrum was washed with three 8 cc. portions of normal saline. These portions were pooled and an assay made for penicillin content. In one experiment 16 to 20 units of penicillin were recovered; in a second 2 to 3 units.

Penicillin may have lodged on the mucous membrane of the nasal passage near the sinus opening and then sucked inside the sinus during the negative pressure cycles.

The inspiration of penicillin aerosol may also have created a venturi effect on the sinus opening and although expiration was through the mouth, traces of penicillin may have drawn into the sinus during succeeding inspirations of aerosol.

A third group of experiments was conducted in order to determine whether or not an aerosol could be expected to deposit on the walls of a sinus if the mist entered the cavity. A nebulizer was connected to a Y two inch diameter rubber tube 35 cm. long. A 10 cc. syringe with piston removed was attached to the other end. The syringe was filled with penicillin aerosol (concentration 50,000 units per cc.) and the contained mist then injected into a rubber catheter immersed in a 25 cc. glass graduate containing glass beads and filled with water. The procedure was repeated forty-five times and the contents assayed for penicillin. Following this the same procedure was

employed but with the catheter in the subject's antrum. After the completion of the procedure the antrum was washed as previously described. These results are seen in Table I.

TABLE I

Date	Interval after Completion of Procedure before Sinus Washed	Total Units of Penicillin Recovered
2/1/46		44– 55 (glass graduate)
2/8/46	5 minutes	31– 41 (in antrum)
2/25/46	2 hours	82–131 (in antrum)
2/26/46	5 minutes	67–105 (in antrum)

These results indicate that penicillin aerosol does lodge on the mucous membrane of the antrum and may be recovered from it from five minutes to two hours after it has been introduced by catheter and syringe.

CLINICAL RESULTS

The clinical results will be presented in the accompanying tables and case reports. These cases represent all cases in which the procedure was tried, including acute and chronic cases, with and without allergic factors as well as infaction.

The clinical results of cases treated in the *hospital* or *at home* two to four times daily are summarized in Tables II and III. Dosage was 50,000 units in 1 cc. normal saline for each inhalation, unless specified differently. Of fifty-eight courses in forty-seven patients, marked improvement took place in eighteen, moderate in seventeen, slight benefit in six and no improvement in seventeen. Of thirty-one patients *x*-rayed before and after treatment, nineteen showed significant improvement on *x*-ray examination, eight no change and four showed increased involvement. In twenty-three cases in which comparative observation was present, the sputum or nasal culture showed disappearance of gram-positive organisms such as: pneumococcus, Streptococcus hemolyticus, Streptococcus viridans, Staphylococcus aureus and Staphylococcus albus in nineteen cases. Out of twenty-seven cases in which cultures were obtained after treatment, gram-negative organisms were found in twenty-four cases.

The clinical results of *clinic* cases treated once daily are summarized in Tables IV and V. Of thirty-five patients, eleven showed marked improvement, thirteen moderate, eight slight and three no improvement. Out of twenty-six patients *x*-rayed before and after treatment, fifteen showed *x*-ray improvement and eleven no improvement. inasal cultures before and after treatment N eighteen cases showed disappearance of some of the gram-positive organisms, but predominance in almost every case of some of the original gram-positive organisms, most frequently Staphylococcus aureus.

The clinical results of cases treated in *office practice* once or twice daily are presented in Table VI. Of twenty-nine courses in twenty-eight patients, ten showed marked improvement, thirteen moderate, three slight, and three no improvement. *X*-rays were taken before and after treatment in eight cases, showing some clearing in five and no change in three.

CASE I. *Chronic Sinusitis and Bronchial Asthma.* A male, thirty-three years of age, had asthma for seven years. Past history included frequent upper respiratory infections and bronchitis in childhood. Allergy history included hay fever in the late summer, and skin sensitivity to numerous allergens. For the past year he had received hyposensitizing injections for ragweed, trees, mixed grasses with little relief. Dyspnea was present on exertion. He admitted having a chronic postnasal discharge with occasional nasal stuffiness and rare headaches.

On admission to the hospital the patient was afebrile. He was moderately dyspneic and wheezed audibly. Significant findings included slight injection of the posterior pharynx with

TABLE II

CLINICAL RESULTS IN HOSPITAL PATIENTS WITH SINUSITIS TREATED WITH PENICILLIN AEROSOL AND NEGATIVE PRESSURE

Case No.	Course	Diagnosis	Additional Penicillin Therapy	Clinical Improvement Attributable to Penicillin Therapy	No. of Daily Inhalations	Duration of Treatment (Days)	Reactions	Remarks
	1	chronic	none	marked	1	10	0	Asthma improved also. Received combination of mouth and nasal penicillin inhalations
(1)	2	chronic	aerosol	moderate	3	21	0	
	3	chronic	aerosol	moderate	3	21	0	
(2)	1	chronic	none	moderate	2	30	0	Previous antral opening
(3)	1	chronic, acute	none	moderate	4	5	0	Required ENT treatments for past few years
	1	chronic	none	marked	4	21	0	Copious amounts of mucopus in trap. Acute infection 2 months after 1st course
(4)	2	chronic, acute	none	marked	4	14	0	
(5)	1	acute	I.M.	none	5 (25,000)	13	Exacerbation of asthma	Allergic rhinitis with superimposed infection.
	1	chronic	oral	marked	2–3	8	0	Had required frequent antral irrigations. Recurrence 7 months later following a common cold. Complete recovery
(6)	2	chronic, acute	none	marked	4	10	0	
	1	chronic	oral	slight	3 (100,000)	19	0	Inadequate suction due to poorly fitting nosepieces.
(7)	2	chronic	none	moderate	1	8	0	Symptomatic moderate improvement on office therapy
(8)	1	chronic	none	none	4	3	0	Course of I.M. penicillin subsequently ineffective
(9)	1	chronic	I.M.	none	5	15	Sore, reddened tongue, aggravation of asthma, urticaria, swollen joints, fever 105°F.	Repeated antral irrigations without improvement in past. Later had bilateral Caldwell-Luc operations. Reaction slowly responded to adrenalin and ephedrine
(10)	1	chronic	none	none	4	10	Exacerbation of asthma	Radical sinus surgery and antral irrigations and polypectomy in past without relief
(11)	1	chronic	oral	none	5	9	Exacerbation of asthma	Repeated antral irrigations in past as well as submucous resection without improvement
(12)	1	chronic	I.M.	marked	4 (100,000)	7	0	After course of therapy bilateral middle turbinectomy performed with removal of some of ethmoid cells. Two months later submucous resection was performed
(13)	1	chronic	I.M.	marked	4 (100,000)	7	0	Sustained improvement
(14)	1	chronic	I.M.	marked	5	23	0	Radical sinus surgery 8 yrs. ago without improvement. Courses of I.M. and oral penicillin prior to admission without benefit. Submucous resection prior to discharge.
	2	chronic	none	marked	4	12	0	Re-entered with only mild symptoms 10 mos. after 1st course

TABLE II (*Continued*)

Case No.	Course	Diagnosis	Additional Penicillin Therapy	Clinical Improvement Attributable to Penicillin Therapy	No. of Daily Inhalations	Duration of Treatment (Days)	Reactions	Remarks
(15)	1	chronic	none	none	4	7	0	Previously had radical sinus surgery. Beeswax penicillin I.M. prior to aerosol. Inhalations caused dyspnea because of emphysema
(16)	1	chronic	oral	none	2	12	0	Inadequate suction due to poorly fitting nosepieces
(17)	1	chronic	I.M.	slight	4	9	0	Previous frontal surgery. Polypectomy subsequent to penicillin therapy
(18)	1	chronic	I.M.	none	4	10	Sore reddened tongue, urticaria, aggravation of asthma	Inadequate suction due to poorly fitting nosepieces
(19)	1	chronic, acute	none	moderate	4 (30,000)	14	0	Multiple allergies
(20)	1	chronic	none	moderate	1	2	0	Previously treated with penicillin aerosol by mouth inhalations for infections asthma. Radical sinus surgery and ENT treatment in past with moderate improvement
(21)	1	chronic, acute	none	moderate	5	8	0	Asthma much improved
	2	acute	none	moderate	1	3	0	
(22)	1	chronic	oral, I.M.	none	4	23	0	Radical sinus surgery in past and repeated antral irrigations, without improvement. Residence in Arizona without benefit
	1	chronic	none	none	4	8	0	Polypectomy several yrs. ago,
(23)	2	chronic	none	none	3	14	0	permanent antral openings,
	3	chronic	none	none	4	21	0	followed by other sinus surgery, no improvement. No relief in Arizona
(24)	1	chronic	none	moderate	4	48	Exacerbation of asthma	Resumed treatment without reaction after interval on sulfacetamide aerosol
	2	chronic	none	moderate	2–3	14		
(25)	1	chronic	oral aerosol	none	2	16	Coated black tongue	Poor suction due to perforated ear drum. Treatment combined with mouth inhalation. Later had polypectomy
(26)	1	chronic, acute	none	marked	4	14	0	Antral irrigations prior to and at start of penicillin therapy. More symptomatic relief and faster *x*-ray clearing after aerosol with suction started
(27)	1	chronic	none	slight	3	21	0	Previously had mouth inhalations for bronchiectasis
(28)	1	chronic, acute	none	marked	2–4 (25,000)	15	Sore nostrils and throat	Sustained improvement for 6 months
(29)	1	chronic	I.M.	slight	3–4	14	0	Asthma relieved by fever therapy
(30)	1	chronic, acute	I.M. for 2 days	marked	2–4	4		Sustained improvement

TABLE II (*Continued*)

Case No.	Course	Diagnosis	Additional Penicillin Therapy	Clinical Improvement Attributable to Penicillin Therapy	No. of Daily Inhalations	Duration of Treatment (Days)	Reactions	Remarks
(31)	1	acute	none	slight	2–3	10	0	Allergic rhinitis with superimposed infection
(32)	1	chronic	none	none	4	14	Exacerbation of asthma	Previously had single daily treatment in clinic for 1 week without improvement. Radical sinus surgery in past with temporary improvement
(33)	1	chronic	I.M. for 2 days	moderate	4–5	10	Urticaria	Reaction occurred after penicillin changed from the calcium to crystalline potassium salt
(34)	1	chronic, acute	none	moderate	4	4	0	Allergic rhinitis
(35)	1	chronic	none	slight	4	12	0	Symptoms of sinusitis without confirmatory *x*-ray evidence
(36)	1	chronic	none	marked	4	21	0	Improvement in symptoms referable to bronchiectasis also
(37)	1	chronic	none	moderate	4	5	0	Previously treated at home with improvement
(38)	1	chronic	none	marked	4	25	0	Marked improvement in asthma also
(39)	1	chronic	none	none	4	14	0	Treated at home, unimproved, required surgery later
(40)	1	chronic, acute	none	marked	4	7	0	Previous I.M. penicillin and antral instillations of penicillin without benefit
(41)	1	acute	none	marked	3–4	10	0	No severe recurrences
(42)	1	chronic	none	none	4	10	0	Increased watery nasal discharge and sneezing. Polypectomy later
(43)	1	chronic	none	moderate	4	20	Sore reddened tongue	Marked improvement at first until reaction occurred. Sulfacetamide substituted. Increased wheezing later
	2	chronic	none	moderate	4	10	0	*X*-ray improvement subsequently when crystalline sodium penicillin used
(44)	1	chronic, acute	oral	moderate	3	12	0	Treatment followed by 15% sulfacetamide aerosol
(45)	1	chronic	none	marked	4	12	Nausea, vomiting and fever	Asthma also improved
(46)	1	chronic	none	marked	4	18	Black coated tongue	Marked improvement sustained 6 months
(47)	1	chronic	none	none	3–4	14	0	Followed tooth infection

lymphoid hyperplasia. Chest showed some increase in the anteroposterior diameter with the use of accessory muscles of respiration and poor diaphragmatic motion. Lungs were hyperresonant with scattered sibilant rhonchi in both phases of respiration.

Laboratory data were as follows: hemoglobin 14.3 Gm., red blood count 5,330,000, white blood count 7,600 with P 53 (0-12-41), L 38, E 16, M 3; ESR 73 mm. after 1 hour. Sputum culture: Streptococcus viridans predominating. Chest *x*-ray revealed increased radiolucency of

TABLE III

X-RAY CHANGES AND SPUTUM CULTURE IN HOSPITAL PATIENTS WITH SINUSITIS TREATED WITH PENICILLIN AEROSOL AND NEGATIVE PRESSURE

Case No.	Course	Sputum Culture		*X*-Ray Examination	
		Before Treatment	After Treatment	Before Treatment	After Treatment
(1)	1	0	0	Pan-sinusitis	0
(2)	1	Proteus, O. pneumoniae	0	Both antra clouded	0
(3)	1	0	0	Diffuse clouding of ethmoids	Clearing of ethmoids
(4)	1	Strep. viridans	B. aerogenes	Diffuse clouding of rt. antrum, slight clouding of lt. antrum and ethmoids, diffuse clouding of sphenoids	Modern clearing of antra and ethmoids, complete clearing of sphenoids
	2			Clouding of both antra	Clearing of antra
(5)	1	Strep. viridans	B. coli	Clear	0
(6)	1	No growth*	B. aerogenes*	Marked clouding of both antra with suggestive fluid levels, clouding of ethmoids, slight clouding of sphenoids	Marked clearing; no evidence of fluid, and only slight residual thickening of lining of antra
	2	0	0	Marked clouding of rt. antrum, mod. clouding of lt. antrum	Clearing of both antra
(7)	1	Pneumococcus, type 19	B. coli	Clouding of all sinuses with fluid levels in antra	Progressively higher fluid levels
	2	Staph. aureus, B. subtilis	0	Clouding of all sinuses	0
(8)	1	B. Friedlander	0	Clouding of left antrum and left ethmoids	0
(9)	1	Non-hemol. Strep.	B. aerogenes B. coli	Marked thickening of lining membrane of both antra, and clouding of all other sinuses	Both antra almost filled with fluid, no change in other sinuses
(10)	1	Strep. viridans	B. coli	Homogeneous dense clouding of all sinuses	No change
(11)	1	Strep. viridans Hemol. Strep.	B. aerogenes	Opaque left frontal, clouding of ft. frontal. Both antra opaque. Clouding of ethmoids and sphenoids	0
(12)	1	B. proteus	B. aerogenes	Clouding of antra, ethmoids and frontals	No change
(13)	1	Staph. aureus* B. coli	0	Clouding of antra and some ethmoid cells	0
(14)	1	Staph. albus	B. aerogenes	Marked thickening of lining membrane of both antra. Clouding of ethmoids	10 days later: Less marked thickening of lining membrane of right antrum
	2	Hemol. Staph. aureus	B. coli	No change	
(15)	1	D. pneumoniae Staph. aureus	B. aerogenes	Pan-sinusitis	No change
(16)	1	B. alkaligenes	0	Pan-sinusitis	No change except development of fluid level in lt. antrum
(17)	1	0	0	Pan-sinusitis	0
(18)	1	Strep. viridans	B. coli	Pan-sinusitis	No change
(19)	1	0	0	Pan-sinusitis	Moderate clearing
(20)	1	0	B. aerogenes	Pan-sinusitis	0
(21)	1	0	0	Moderate clouding of both antra	Clearing of antra
	2	Hemol. Strep. D. pneumoniae†	0	Clouding of antra	0
(22)	1	Hemol. B. pyocyaneus	B. aerogenes	Pan-sinusitis	0
(23)	1	0	B. aerogenes	Pan-sinusitis	No change
	2	B. aerogenes	0		
	3	0	Staph. auerus	Pan-sinusitis	0

* Nasal culture.
† Throat culture.

TABLE III (*Continued*)

Case No.	Course	Sputum Culture		*X*-Ray Examination	
		Before Treatment	After Treatment	Before Treatment	After Treatment
(24)	1	Strep. viridans	0	Pan-sinusitis	Very slight clearing
	2	Staph. aureus	0	Pan-sinusitis	Slight clearing
(25)	1	Strep. viridans	Hemol. B. coli	Pan-sinusitis	0
(26)	1	Strep. viridans* Hemol. Staph. albus	0	Marked clouding of both antra	Clearing of antra
(27)	1	D. pneumoniae Staph. aureus Non-hemol. Strep.	D. pneumoniae	Pan-sinusitis	Pan-sinusitis less marked than prior to therapy
(28)	1	Strep. viridans Hemol. Strep. Staph. aureus	Yeasts	Marked thickening of lining membrane of both antra with clouding of ethmoids bilaterally	Complete clearing of rt. antrum and ethmoid cells with only slight clouding of inferior portion of lt. antrum
(29)	1	B. coli	Gram. neg. rods	Clouding of antra	0
	2	D. Pneumoniae Staph. aureus	Non-hemol. Strep.		
(30)	1	No growth†	0	Clouding of ethmoids	0
(31)	1	Hemol. Strep. †	N. catarrhalis†	Slight thickening of lining membrane of both antra, right ethmoids clouded	0
(32)	1	Overgrown with proteus	B. aerogenes	Pan-sinusitis	No change
(33)	1	Slight growth†	0	Pan-sinusitis	No change
(34)	1	No growth*	0	Left frontal and right sphenoid slightly clouded	0
(35)	1	No growth*	0	Negative	0
(36)	1	Hemol. Strep.* Hemol. Strep†	Negative for Hemol. Strep.	Pan-sinusitis	Increase in size of polypoid mass in lt. frontal and rt. antrum
(37)	1	0	0	Clouding of antra	Some clearing
(38)	1	Strep. viridans Staph. aureus	Gram. neg. bacillus	Pan-sinusitis	No change
(39)	1	0	0	Pan-sinusitis, opaque left antrum	0
(40)	1	Pneumococcus	0	Opaque antra; ethmoids, frontals and sphenoids slightly clouded	Progressive clearing
(41)	1	0	0	Clouding of both antra	0
(42)	1	Hemol. Strep. Pneumococcus Staph. aureus	0	Clouding of both antra, slight clouding of ethmoids	0
(43)	1	Staph. aureus Non-hemol. Strep. Hemol. Strep.	0	Marked thickening of lining membrane of both antra. Ethmoids slightly clouded on left	
	2	Gram neg. bacillus	0	Marked thickening of lining membrane of rt. antrum and clouding of left antrum	Improvement
(44)	1	Strep. viridans	B. coli	Marked clouding of rt. antrum, slight thickening of lining membrane of lt. antrum and ethmoids on right. Slight clouding of left frontal	Some clearing of rt. antrum with better aeration
	2	Staph. aureus D. pneumoniae Hemol. Strep.	B. coli		
(45)	1	Hemol. Strep. Non-hemol. Strep. Hemol. Staph. aureus Staph. aureus	0	Clouding of antra and ethmoids bilaterally	Slightly better aeration of right antrum
(46)	1	Hemol. Strep. Non-hemol-Strep. Staph. albus	0	Marked clouding of rt. antrum; slight clouding of lt. antrum. Right ethmoids slightly clouded	Marked improvement
(47)	1	Staph. aureus	B. coli	0	0

TABLE IV

CLINICAL RESULTS IN CLINIC PATIENTS WITH SINUSITIS TREATED WITH PENICILLIN AEROSOL AND NEGATIVE PRESSURE

Case No.	Diagnosis	Clinical Improvement Attributable to Penicillin Therapy	Total No. of Inhalations	Duration of Treatment (Days)	Remarks
1	Chronic	slight	26	44	Additional allergic factors. Improvement not sustained. Asthma also improved on therapy
2	Acute	none	23	42	Allergic rhinitis underlying infection
3	Chronic	moderate	5	6	Patient returned for second course which was followed by moderate improvement
4	Chronic	moderate	14	21	Polyps and asthma. Asthma slightly improved
5	Acute	marked	3	3	
6	Chronic	marked	9	10	
7	Chronic	marked	5	5	
8	Acute	moderate	6	7	
9	Chronic	moderate	11	15	
10	Chronic	moderate	7	8	Marked symptomatic improvement
11	Chronic, acute	marked	7	12	Improvement sustained several months
12	Chronic	moderate	8	12	
13	Chronic	moderate	20	30	
14	Acute	marked	8	8	
15	Chronic	marked	23	31	
16	Chronic	none	6	8	Hospitalization necessary
17	Chronic	slight	20	30	
18	Chronic	none	35	48	Slight improvement at first, later worse. Operation: antral windows
19	Chronic	moderate	18	40	Improved until sensitivity reaction
20	Chronic	slight	10	14	Later had marked improvement in hospital on 4 daily inhalations. Asthma greatly improved. Effect not sustained over 1 month
21	Chronic	moderate	65	140	Improvement not sustained following treatment. Asthma markedly improved. Later required antral washings
22	Chronic	marked	4	5	Improved markedly but had penicillin sensitivity reaction
23	Acute	marked	6	14	Dramatic improvement
24	Chronic	slight	8	15	
25	Chronic	marked	2	2	Marked improvement, but patient had antral washing
26	Chronic	moderate	4	7	
27	Chronic	moderate	10	17	
28	Chronic	marked	8	21	
29	Chronic	slight	15	28	
30	Acute	marked	9	14	
31	Chronic	moderate	20	30	
32	Chronic	slight	4	5	Sensitivity reaction to both penicillin and sulfacetamide
33	Chronic	slight	10	14	
34	Chronic	moderate	7	9	
35	Chronic	slight	3	4	

both lung fields. Sinus *x*-rays revealed clear frontals, diffuse clouding of the right antrum and probable slight thickening of the mucosal lining of the left antrum, slight clouding of the ethmoids on the right and diffuse clouding of both sphenoids. (Figs. 3 and 4.)

The patient was given a course of nasal penicillin aerosol with negative pressure, 50,000 units (concentration of 20,000 units per cc. normal saline) four times a day for three weeks or a total of 4,000,000 units. He used 2 drops of privine 0.1 per cent instilled into each nostril before penicillin inhalations. A large amount of mucopurulent secretion was obtained in the

TABLE V

X-RAY CHANGES AND NASAL CULTURE IN CLINIC PATIENTS WITH SINUSITIS TREATED WITH PENICILLIN AEROSOL AND NEGATIVE PRESSURE

Case No.	Nasal Culture		*X*-Ray Examination	
	Before Treatment	After Treatment	Before Treatment	After Treatment
1	Strep. viridans Staph. aureus	Staph. aureus	Pan-sinusitis	Slight clearing
2	Hemol. Staph. aureus D. pneumoniae	D. pneumoniae	Rt. frontal Rt. maxillary Rt. ethmoiditis	No change
3	D. pneumoniae Staph. aureus		Pan-sinusitis with fluid in antra	Clearing except for right frontal
4	Staph. aureus Hemol. Staph. aureus		Maxillary sinusitis, bilateral	No change
5	Hemol. Strep. Staph. aureus	Staph. aureus	Ethmoid and maxillary sinusitis, bilateral	Clearing of ethmoids, partial clearing of antra
6	Staph. aureus		Maxillary sinusitis, bilateral	0
7	Hemol. Staph. aureus	No growth	Fluid in rt. frontal and rt. antrum	Some clearing
8	Hemol. Strep.		Maxillary sinusitis, bilateral	Slight clearing of right maxillary
9	Pneumococcus, type 7 Staph. albus Non-hemol. Strep.	Staph. aureus	Maxillary sinusitis, bilateral	Slight clearing on right
10	Staph. aureus		Maxillary sinusitis, bilateral	Clearing
11			Bilateral clouding of antra, esp. rt.	Clearing
12	D. pneumoniae Staph. aureus	Staph. aureus	Maxillary, bilateral and left sphenoid sinusitis	No change
13	Staph. aureus	Staph. aureus	Rt. maxillary sinusitis	No change
14			Lt. frontal, rt. maxillary and bilateral ethmoiditis	No change
15	Staph. aureus	No growth	Maxillary and ethmoiditis	No change
16	Strep. viridans		Anomalous development, no maxillary sinus	0
17	Staph. aureus Hemol. Staph. aureus Hemol. B. coli Step. viridans	Staph. aureus	Maxillary and ethmoid sinusitis	
18	Non-hemol. Strep. Staph. aureus	D. pneumoniae Staph. aureus Non-hemol. Strep.	Pan-sinusitis	Frontals involved later
19	Negative for hemol. Strep.	Hemol. Staph. aureus Staph. aureus	Pan-sinusitis	Clearing of right maxillary sinus
20	Hemol. Strep. Staph. aureus	Staph. aureus	Pan-sinusitis	No change
21	Staph. aureus Hemol. Staph. aureus	Staph. aureus Non-hemol. Strep.	Ethmoiditis	No change
22	Hemol. Staph. aureus	Hemol. Strep. Staph. aureus	Bilateral ethmoid, sphenoid and maxillary sinusitis	Some clearing
23	Staph. aureus		Clouding of ethmoids and lt. antrum	0
24	Staph. aureus	Staph. aureus	Bilateral maxillary sinusitis	0
25	Negative for Hemol. Strep.		Pan-sinusitis	Clearing
26	Pneumococcus, type 3		Pan-sinusitis	0
27	Pneumococcus, type 3	Staph. aureus	Pan-sinusitis	No change
28	D. pneumoniae Hemol. Staph. aureus	Staph. aureus	Pan-sinusitis	Complete clearing
29	Staph. aureus	Staph. aureus	Pan-sinusitis	Slightly improved
30	Hemol. Strep.		Left maxillary sinusitis	0
31	Staph. albus		Chronic antral disease	
32	Non-hemol. Strep. Staph. aureus		Opaque rt. antrum	Improved
33	Gram pos. bacilli		Maxillary sinusitis, chronic, bilateral	Slightly improved
34	Gram pos. bacilli Gram neg. diplococcus	Gram neg. bacilli	Maxillary sinusitis, bilateral with fluid level on right	Right antrum completely opaque. Some clearing of left antrum
35	Staph. albus Hemol. Strep.	Staph. aureus	Thickened membrane of both antra	0

TABLE VI

CLINICAL RESULTS IN OFFICE PATIENTS WITH SINUSITIS TREATED WITH PENICILLIN AEROSOL AND NEGATIVE PRESSURE

Case No.	Diagnosis	Sputum Culture Before Treatment	*X*-Ray Examination Before Treatment	Clinical Improvement Attributable to Penicillin Therapy	Total No. of Inhalations	Duration of Treatment (Days)	Remarks
1	Chronic, acute	Hemol. Staph. aureus † Strep. viridans Staph. aureus	Thickened membrane and fluid level in right antrum. Ethmoids and frontal clouded on left. Thickened membrane of left antrum	Moderate	3	3	*X*-ray clearing of left antrum. Asthma improved
2	Chronic, acute	Staph. aureus *	Clouding of both antra and left ethmoids	Moderate	15	10	
3	Chronic	Staph. aureus Non-hemol. Strep.	Marked clouding of rt. antrum, mod. lt. antrum, lt. ethmoid hazy	None	22	17	Temporary improvement. Dyspneic from inhalations because of emphysema
4	Chronic	Strep. viridans	Moderate clouding of antra, ethmoids slightly clouded	Marked	10	14	Marked improvement in sense of well being, loss of fatigue and anorexia
5	Chronic	Strep. viridans H. influenzae	Clouding of both antra and ethmoids	Moderate	9	14	Numerous antral irrigations in past. *X*-ray after treatment unchanged
6	Chronic	Strep. viridans Hemol. strep.	Clouding of both antra and left ethmoids	None	10	14	Symptomatic improvement during treatment, not sustained. No *x*-ray improvement. Required submucous resection and ethmoidectomy
7	Acute	Staph. aureus D. pneumoniae	Thickened membrane of right antrum and slightly of left antrum. Ethmoids clouded	Marked	5	7	Recurrence treated with two subsequent inhalations
8	Chronic		Opaque antra and ethmoid on left	Moderate	5	5	
9	Chronic		Thickening of membrane of both antra	Slight	3	3	
10	Acute	Hemol. Strep. Pneumococcus Staph. aureus	Clouding of left ethmoid	Moderate	5	5	
11	Chronic, acute	B. coli	Both antra, left frontal hazy	Marked	2	2	Clearing of both antra by *x*-ray
12	Chronic	H. Staph. aureus	Clouding of both antra	Moderate	14	7	Broncho-spasm during inhalations
13	Chronic	Strep. viridans Hemol. Strep.	Thickened membrane of both antra	Marked	10	14	
14	Chronic 1st course	Hemol. Strep. Strep. viridans	Bilateral maxillary clouding, ethmoids clouded	None	10	14	Symptoms aggravated by positive pressure
	Chronic 2nd course	Strep. viridans Hemol. Strep. Staph. albus	No change	Moderate	10	14	*X*-ray after treatment. Slight reduction in thickening of lining membrane of both antra

* Nasal culture.
† Throat culture.

TABLE VI (*Continued*)

Case No.	Diagnosis	Sputum Culture Before Treatment	*X*-Ray Examination Before Treatment	Clinical Improvement Attributable to Penicillin Therapy	Total No. of Inhalations	Duration of Treatment (Days)	Remarks
15	Chronic, acute	Hemol. Strep. Strep. viridans Staph. aureus	Clouding of left antrum	Moderate	14	7	
16	Chronic		Clouding of both antra	Moderate	28	14	
17	Chronic	Hemol. Strep. Strep. viridans Micrococos	Thickened membrane of both antra, clouding of left frontal and left ethmoids	Moderate	9	14	Sustained improvement for several months with concomitant improvement in asthma
18	Chronic	Staph. aureus D. pneumo†	Diffuse clouding of left antrum, thickened membrane of right antrum	Slight	7	9	
19	Chronic	Strep. viridans Non-hemol. Strep.	Clouding of inferior portion of rt. antrum	Slight	10	5	
20	Acute	0	Clouding of both antra and ethmoids	Marked	4	6	Clinical recovery. Asthma relieved
21	Chronic, acute		Thickened membrane of both antra	Marked	10	12	Clinical recovery
22	Chronic	Staph. albus* Staph. aureus* Strep. viridans Hemol. Staph. aureus	Markedly thickened membrane of lt. antrum, and slightly of rt. antrum. Some clouding of rt. ethmoids and left frontal	Marked	14	14	*X*-ray after treatment: Some improvement
23	Chronic	0	Homogeneous clouding of both antra, frontals and ethmoids	Marked	5	14	Symptomsaggravated following submucous resection two years ago
24	Chronic, acute	Non-hemol. Strep. Staph. aureus D. pneumococcus	Thickened membrane of both antra, ethmoids clouded	Moderate	60	21	Culture unchanged. Marked improvement in first 2 wks., when developed an acute infection which responded less well to treatment
25	Chronic, acute	Hemol. Strep. Staph. aureus D. pneumoniae	Clouding of both antra and left ethmoids	Moderate	10	14	*X*-ray after treatment unchanged. Previously had no symptomatic improvement with nasal penicillin by atomizer spray
26	Chronic	No growth	Clouding of rt. antrum, thickening of lining membrane of left antrum, ethmoids clouded	Marked	23	15	Culture after treatment: Gram neg. rod. *X*-ray after treatment: some clearing
27	Chronic, acute	0	Slight clouding of antra and ethmoids	Moderate	28	20	Had nausea, chilliness and fever after 1st few inhalations, later no reaction
28	Chronic, acute		Marked clouding of right antrum	Marked	10	5	

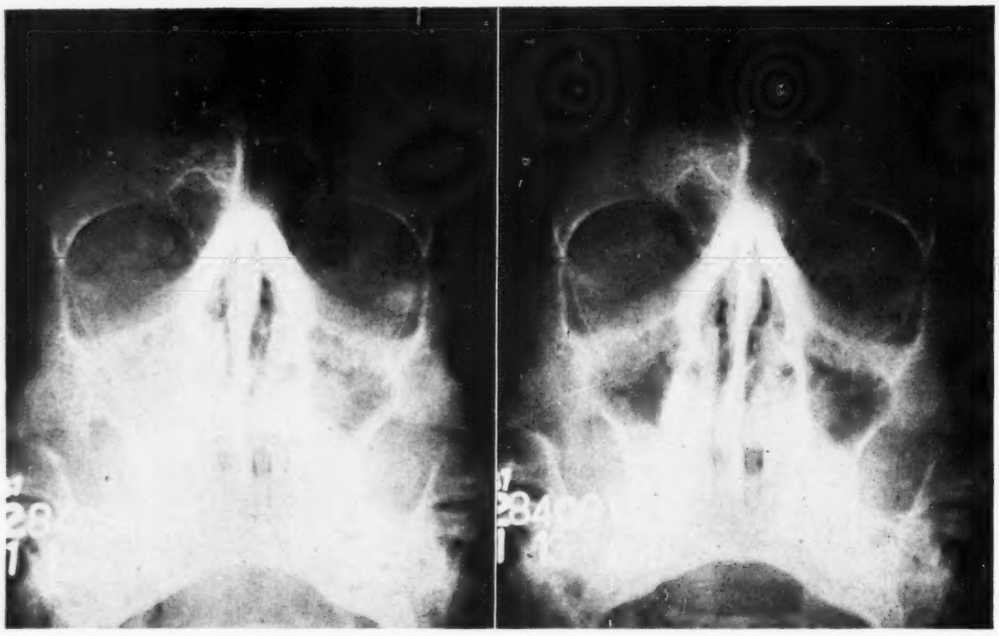

FIG. 3. *X-rays of sinuses before treatment (left) and eight days after start of treatment (right), revealing marked clearing of right antrum and slight clearing of left antrum.*

trap of the apparatus. The only other medication consisted of oral aminophyllin, ephedrine, potassium iodide and nebulized Vaponefrin.

There was marked relief of symptoms of asthma and sinusitis. Nasal passages became clear and there was little post-nasal drip. The course was afebrile. Cough and expectoration decreased about 75 per cent. Dyspnea was not observed except on undue exertion. Mild wheezing occurred infrequently. Sputum culture showed Bacillus aerogenes predominating. ESR fell to 17 mm. after one hour. Lungs were clear on physical examination, although breath sounds were distant. Sinus *x*-rays eight days after starting penicillin nasal suction treatment revealed considerable clearing of the clouding previously noted in the right antrum, right ethmoids and complete clearing of the sphenoids.

Following discharge, the patient remained well for two and one-half months with occasional use of Vaponefrin spray and oral aminophyllin. At that time he developed an acute sinusitis with frontal headache, nasal obstruction and mucopurulent discharge. There was some exacerbation of his asthma. The sinus *x*-rays revealed clouding of both antra although the sphenoids remained clear. (Fig. 5.) He was treated at home with a course of nasal penicillin aerosol with negative pressure, 50,000 units in 1 cc. normal saline four times a day for a total of ten days or 2,000,000 units. At that time his symptoms had entirely disappeared and his sinus *x*-rays showed clearing. The patient has remained well during the three months since the second course of treatment and has been doing eight hours of sedentary work daily.

CASE II. *Chronic Sinusitis.* A white, married woman, forty years of age had a history of sinusitis ten years ago. Since that time she had no acute symptoms until one week before office consultation when following a cold she complained of nasal discharge and obstruction, intermittent headache and slight fever to 99.4°F. She was put at rest in bed, penicillin was administered 20,000 units intramuscularly every three hours, and penicillin aerosol 50,000 units per cc. was inhaled every three hours during the day *without* negative pressure. In addition, penicillin was instilled by a nose and throat consultant three times during this period of seven days' treatment.

At the end of one week of combined therapy the patient's symptoms persisted; *x*-ray of the sinuses revealed diffuse clouding of the antra as seen in the accompanying photograph. (Fig. 6.) Penicillin by intramuscular injection

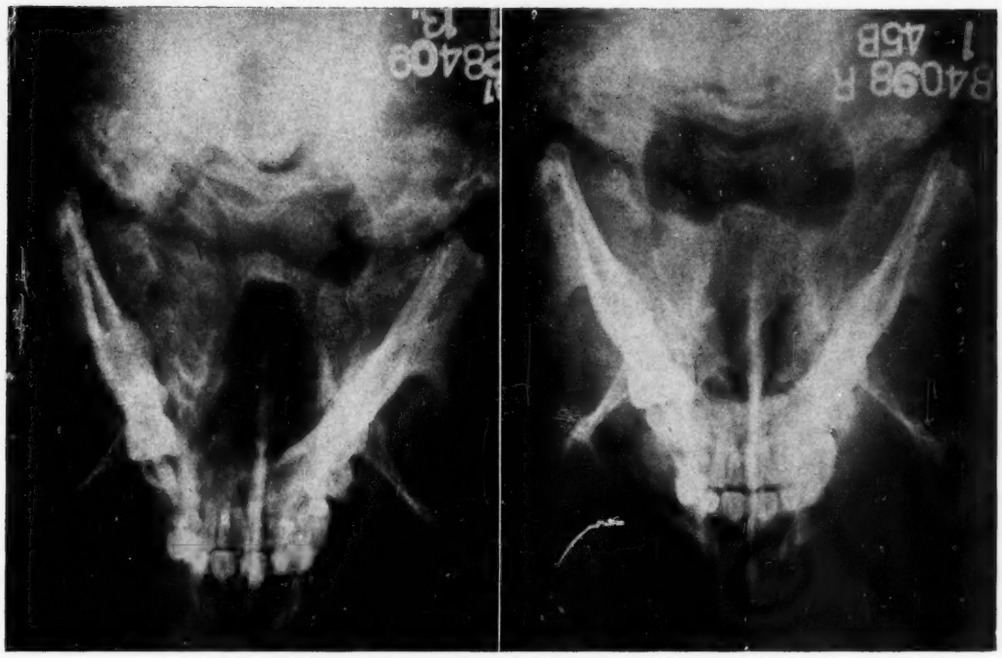

FIG. 4. *X-rays of sinuses before tretament (left) and eight days after start of treatment (right), revealing complete clearing of the sphenoids.*

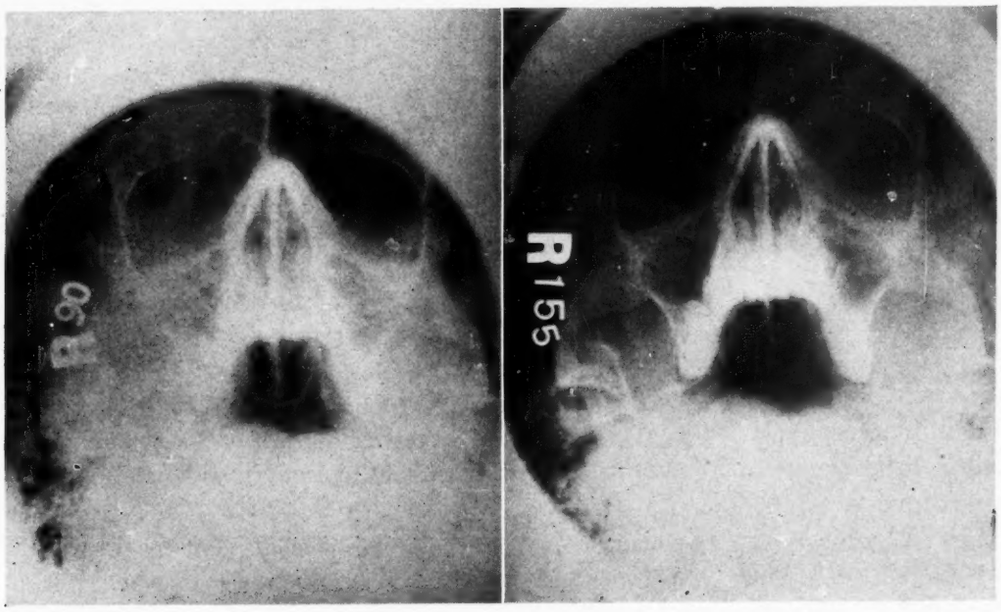

FIG. 5. *Sinus x-rays before second course of treatment (left) and after treatment (right) showing moderate clearing of both antra.*

was then stopped as well as instillations into the antra. The patient was then given four inhalations of 50,000 units of penicillin per cc. normal saline with negative pressure, the oxygen flow being maintained at 6 liters per minute. Improvement began in two days and was progressive from then on, no symptoms being present at the end of seven days; treatment was stopped and the subsequent *x*-ray showed improvement. An *x*-ray one month afterwards revealed further clearing of the process in both sinuses except for what was interpreted as a polypoid formation in the mucous membrane in the lower part of both antra.

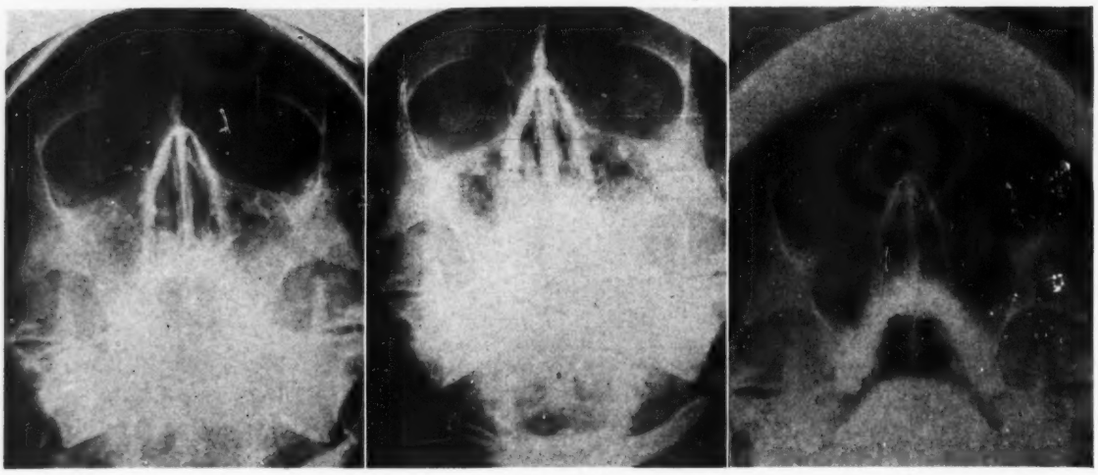

FIG. 6. *Sinus x-rays after one week of control therapy (left), after one week of penicillin aerosol with negative pressure (center) and one month later (right) showing progressive clearing.*

The patient was well for eight months when an acute sinusitis took place swiftly after a head cold. *X*-ray of the sinuses showed a slight diffuse clouding of both antra. She was treated with inhalation of 50,000 units of penicillin per cc. normal saline with negative pressure, once a day for two days when symptoms cleared and the patient refused further therapy or *x*-ray examination. She has been clinically well for the seven months since then.

Comment. In this patient a control period of intramuscular injection and nasal inhalation of penicillin, combined with instillation of penicillin in solution, 500 units per cc. into the antra, was carried out without clinical benefit. The subsequent treatment with penicillin aerosol and negative pressure brought prompt relief with symptomatic complete recovery.

CASE III. *Chronic and Acute Sinusitis.* A female, thirty-three years old, gave a history of recurrent sinusitis of ten years' duration. During the previous two weeks she complained of increasing headache, obstruction and discharge. *X*-ray showed bilateral involvement, especially the right antrum. Ear, nose and throat examination revealed bilateral overflow of mucopurulent secretion. She was treated in the clinic receiving seven treatments in twelve days, one treatment per day, 40,000 units per cc. normal saline. *X*-ray and ENT examination showed clearing of the infection. (Fig. 7.)

CASE IV. *Chronic Sinusitis and Pulmonary Emphysema.* A male, fifty years of age was admitted to the hospital for oxygen therapy because of pulmonary emphysema. He had a history of sinusitis for many years with symptoms of headache, nasal obstruction, post-nasal discharge. History includes arrested tuberculosis of the left upper lobe.

The patient was a well developed, well nourished middle-aged man moderately dyspneic in the oxygen chamber (concentration 50 per cent). No cyanosis was present. The pharynx was moderately reddened. The chest was barrel-shaped and the patient used the accessory muscles of respiration. Lungs were resonant except for slight dullness at the left posterior top. Expiratory note was prolonged and breath sounds were diminished and distant throughout both lungs. A few subcrepitant râles, increased after cough, were audible on the left posteriorly above D 5.

Laboratory data were as follows: hemoglobin 17.7 Gm., red blood count 6,280,000, white blood count 9,550 with P 52 (0-2-50), L 31, M 15, B 2; ESR 25 mm. after one hour; serum CO_2 62.6 volumes per cent. Sputum culture revealed Staphylococcus aureus and non-hemolytic streptococcus. *X*-ray of the chest revealed mottled fibrotic infiltration in the upper one-third of the left lung field; emphysematous appearance of remainder of the lung fields with

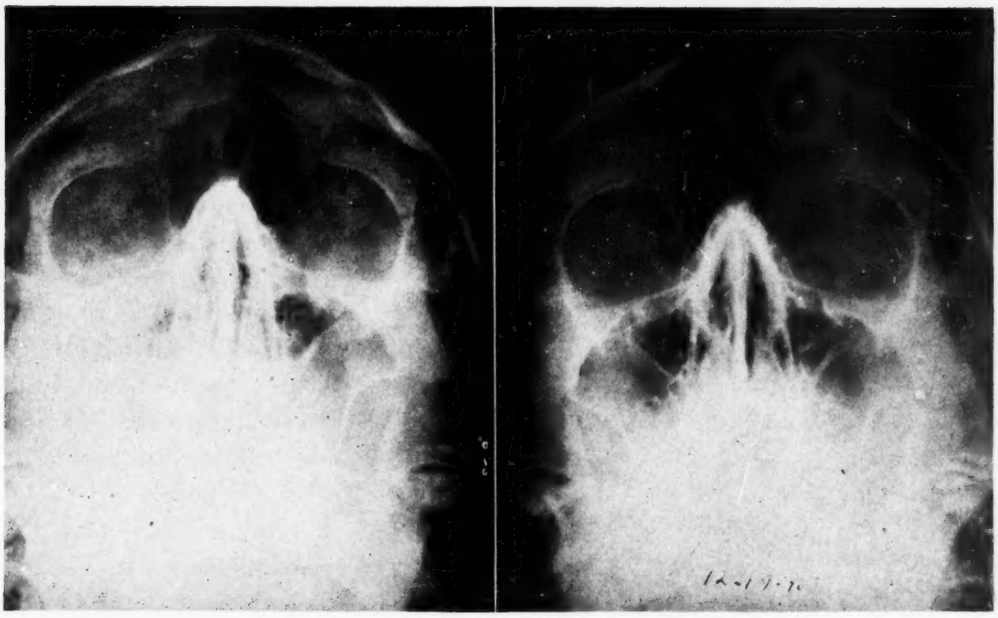

FIG. 7. *X-rays of sinuses before treatment (left) and after treatment (right), revealing moderate antral clearing with some residual thickening of the lining membrane.*

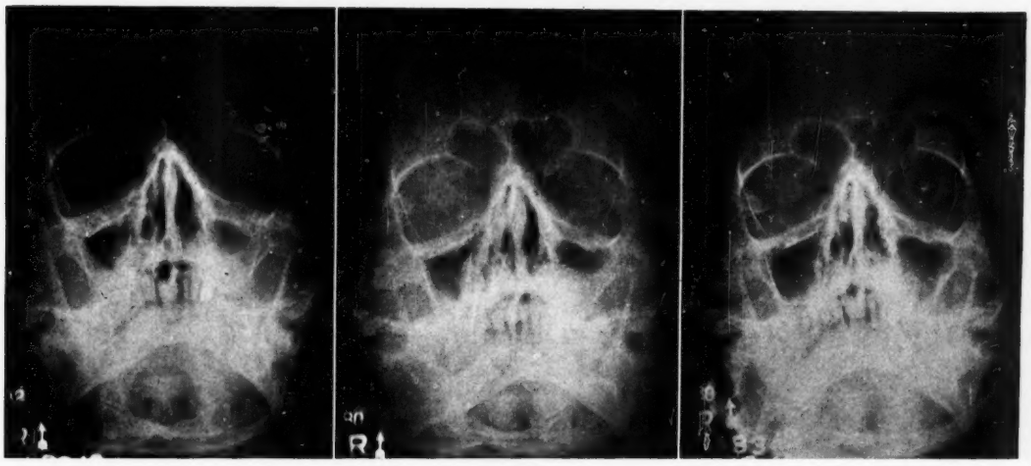

FIG. 8. *Sinus x-rays before treatment (left), during treatment (center), and after treatment (right) showing increased involvement of left antrum eight days after start of therapy but final complete clearing of right antrum with moderate clearing of left antrum.*

bullae. Sinus *x*-ray showed considerable thickening of the lining membrane of both antra with clouding of the ethmoid cells on the right and a lesser clouding on the left. (Fig. 8.)

Combined penicillin oral inhalations and nasal inhalations with negative pressure were given for a nine-day period, the patient receiving a total of 400,000 units (40,000 units once or twice daily), by oral and 600,000 units (25,000 units two to three times daily) by nasal inhalation. At this time the sinus films showed no change in the right antrum or ethmoids, but a further increase in density with suggestion of fluid in the left antrum, although the air-containing portion appeared clearer. Sputum culture showed Streptococcus viridans. Serum CO_2 rose to 69.2 volumes per cent. The patient was discharged to continue nasal inhalations at home since his pulmonary status was markedly improved. He was afebrile throughout his hospital stay.

He was re-admitted four days later because of acute overdistention of the lungs, apparently precipitated by undue exertion. Nasal penicillin

aerosol was stopped two days later because of soreness and redness of the nostrils and sore, reddened throat, as well as evidence of bronchospasm. Sinus *x*-rays, however, showed complete clearing of the right antrum and ethmoid cells, with only slight clouding of the inferior portion of the left antrum persisting. (Fig. 8.) Bronchopulmonary symptoms responded in several days to therapy with continuous oxygen, demerol, aminophyllin, ephedrine and Vaponefrin-neosynephrine spray. The patient was discharged in two weeks markedly improved. Sinus *x*-rays two months later showed maintenance of improvement.

A patient was seen recently in whom symptoms of sinusitis of four weeks' duration were present combined with cough and expectoration of considerable quantities of mucopurulent material. A hemolytic staphylococcus aureus was isolated from the sputum and from a nasal culture. She was treated with one inhalation a day of penicillin aerosol, containing 50,000 units per cc., with negative pressure for four days. At the same time aminophyllin 0.2 Gm. was prescribed on arising and at 3 P.M. demerol was administered by mouth, 50 mg. after lunch and on retiring. Within a period of five days the cough, expectoration, nasal discharge and obstruction had almost entirely disappeared. No further follow-up was possible since she decided that she was clinically well, although *x*-ray had previously shown marked clouding of both antra.

COMMENTS

The results presented above indicate that acute and chronic sinusitis may in some cases be effectively treated by nasal inhalation of penicillin aerosol in conjunction with negative pressure in the nasal passages and sinuses.

Difficulties are inevitably encountered in appraising the value of any new therapeutic procedure. In the treatment of sinusitis primary consideration must be given not only to the infectious agent, but to the presence of allergic factors. In patients with acute sinusitis *without* hypersensitivity to dust and other inhalants therapeutic benefit may be achieved in a variety of ways. Rest in bed, application of vasoconstricting solutions or inhalations of steam are followed in some cases by recovery. In other cases, washing out the antra through the natural orifice results in adequate drainage and prompt recovery. The intention of this presentation is not to suggest that penicillin aerosol with negative pressure is necessarily better than other forms of treatment, but that it is an additional procedure that may be used in infectious sinusitis and that it has been found to be of therapeutic value in acute, subacute and chronic cases.

Patients with chronic sinusitis frequently reveal both an allergic and infectious etiology. Patients in this category who have been treated once a day in the clinic have frequently shown little or no benefit. Others who have been treated three to four times a day have shown moderate improvement but with a tendency to relapse. In cases sensitive to cat hair or other substances allergic swelling of the nose may interfere with antral drainage and predispose to subsequent infection. However, patients with chronic purulent sinusitis who have been previously treated by antral irrigations with only temporary benefit and with persisting symptoms and pathological conditions in the sinuses have in some instances obtained marked and prolonged benefit. These patients are not considered permanently cured as reinfection may take place.

In cases of sinusitis with associated bronchitis aminophyllin is generally of significant therapeutic value in relieving cough, even without overt signs of bronchospasm such as sibilant râles. Demerol is generally more effective than codiene, and the combination of demerol and aminophyllin is frequently of dramatic value in the treat-

ment of acute and subacute as well as chronic bronchitis. When demerol is administered by mouth it is important that the patient rest for two hours after ingestion in order to avoid symptoms of dizziness.

The complication of urticaria may take place but this is infrequent and may now be effectively handled by administration of benadryl. Patients with an allergic history are more apt to develop urticaria than those with a purely infectious basis.

In our experience calcium penicillin has been better tolerated than the sodium salt, and at present crystalline penicillin seems preferable to either.

Although a blood level of 0.1 to 0.2 units per cc. of serum is generally obtained with oral inhalation of penicillin aerosol, the use of this dosage with the negative pressure rebreathing device does not result in sufficient absorption through the lungs to provide any more than a minimal (0.025 to 0.05 U/cc. serum) or no detectable blood level. We have previously shown that the amount of penicillin in the blood is substantially less when inhalation of penicillin takes place through the nose instead of the mouth.

Since negative pressures of 50 to 60 mm. Hg are intermittently produced in the antrum by the technic employed, it is evident that aeration of the sinuses takes place with replacement of penicillin mist for the air previously present in the antral cavity. To what extent therapeutic results may be obtained by intermittent negative pressure itself has not been determined but it seems a sounder practice to facilitate the deposition locally of penicillin particles. Studies are in progress in which other chemotherapeutic aerosols are used, such as 5 per cent sulfathiazole, 15 per cent sulfacetimide, 0.25 per cent p-chlorophenol and streptomycin. Evidence has been presented that the therapeutic agent does actually lodge in infected mucous sinus membrane since antral washings have contained penicillin after this type of treatment. Since there is no way of determining how much penicillin is absorbed from the membrane before the washings, or how much clings to the mucous membrane after the washing, the concentration of penicillin in the antrum cannot be determined.

SUMMARY

Nasal inhalation of penicillin aerosol in conjunction with negative pressure in the nasal passages has been described as a treatment for acute and chronic sinusitis. An apparatus which also produces a slight positive pressure in addition to negative pressure during inhalation of penicillin nebulin is reported.

A negative pressure in the antra of 50 to 60 mm. Hg has been demonstrated with the procedure used. Washings from the antrum in selected cases revealed that penicillin was introduced following inhalation of 50,000 units of penicillin aerosol in conjunction with repeated negative pressure.

Cases of acute paranasal sinusitis are reported in which clinical recovery took place with one to four treatments per day over a period of three days to two weeks. Patients with chronic sinusitis are described in which marked improvement was demonstrated by *x*-ray and clinically with four treatments daily over a period of twelve days or more. Cases with chronic paranasal sinusitis treated once a day have frequently shown little or no significant benefit. In those patients in whom allergy is a prominent etiological factor less favorable results may be expected. Clinical improvement has been obtained in cases in which both infectious and allergic causal factors were definitely present.

Inspection of the tables and case reports illustrates the effect on the course of the disease in individual patients; a summary of the clinical results may be stated as

follows, using the combined findings of hospital, home, clinic and office patients: Of 122 courses of therapy in 110 patients, marked improvement took place in thirty-nine, moderate in forty-three, slight in seventeen and no improvement in twenty-three.

Of sixty-five patients *x*-rayed before and after treatment, marked or significant improvement was observed in thirty-nine, no improvement in twenty-two and progressive involvement in four.

In forty-one patients in whom comparative cultures of the nasal or sputum cultures were available, disappearance of gram-positive organisms found prior to treatment took place in twenty-four. In twenty-five of these cases gram-positive organisms were found after treatment, either as the predominating organisms or in significant numbers.

The method of treating sinusitis by penicillin aerosol and negative pressure appears to be a practical procedure that produces little or no discomfort.

This report is intended as an exploratory study on the principles, methods and early clinical results of its use rather than as any final appraisal of its value.*

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Conference on Therapy

Treatment of Coronary Artery Disease*

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. The next report will appear in the November issue and will concern a continuation of the same topic.

DR. HARRY GOLD. There are several clinical varieties of coronary artery disease. Pain in the precordial or substernal region, or other areas of the chest, presents one of the chief problems. The pain is linked to a variety of factors. There is the pain associated with emotion or physical exertion, particularly walking, as occurs in the more usual type of angina of effort. There are those in whom attacks of pain frequently occur while the patients are at rest and awaken them at night, the pain of angina decubitus. There is the attack of acute coronary thrombosis or myocardial infarction. Pain, however, is not the sole problem in the management of coronary artery disease. Although there is a good deal of overlapping in the therapeutic problems presented by the clinical varieties of coronary artery disease, several of them present problems peculiar to themselves and require special attention. The list of drugs is a fairly large one; it includes morphine, demerol, codeine, barbiturates, nitrites, aminophylline, papaverine, quinidine, digitalis, mercurial diuretics and others. Views concerning the methods of their use and their value are not entirely in accord. How the evidence stands may emerge from the discussion in the conference today. Dr. Eggleston will make the opening remarks.

DR. CARY EGGLESTON: Dr. Gold left out one form of coronary artery disease the treatment of which might be discussed, namely, that form which is discovered in the asymptomatic stage. Coronary artery disease is probably the most prevalent of all forms of heart disease and certainly is the most prevalent past the age of fifty. It may exist for a long time before any particular symptoms direct the patient's attention to the disease. From the point of view of therapy, however, we can confine our discussion largely to the types that Dr. Gold has just mentioned.

The anginal syndrome, or angina pectoris, or pain in the chest secondary to coronary artery disease, occurs most commonly as the result of effort. On the basis of rather critical and extensive analysis it is believed to be due primarily, or chiefly, to a relative myocardial anoxemia, that is, a reduction in the amount of oxygen carried to the heart muscle in relation to the amount of work that the muscle is being called upon to do. Consequently, it is commonly associated with effort or other factors which increase heart work. We cannot afford to overlook the fact that emotional stresses and strains, that a distended abdomen from any cause whatsoever, that reduction in the oxygen carrying power of the blood by anemias, and the like, are all mechanisms working in the same direction and all may

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be productive of angina pectoris or the anginal syndrome in the susceptible individual. In addition to this, the state of the nervous system is of great importance to the patient who is a victim of angina. That this plays a rôle is indicated by the relative rarity of angina in phlegmatic individuals, and by its increased incidence in patients who are of a high-strung, emotional, nervous temperament. This, undoubtedly, is a factor of some importance in the frequency of recurrence of anginal seizures. Patients who are overweight not infrequently are subject to angina, but the syndrome by no means spares the underweight or lean. Changes in temperature, sudden cold, chilling, wind and particularly cold wind, precipitate anginal seizures. Other more or less trivial factors of causation may be passed over so that we may approach immediately the question of management.

Before drug therapy is considered one should have made a critical analysis of the factors which induce anginal seizures in the individual patient and then set about by a process of education and analysis of the situation pertaining to that individual patient, to eliminate as many of those precipitating factors as possible. After this has been accomplished—and its accomplishment depends, in large measure, on the cooperation of the individual, and that, in turn, is related to his intelligence and his ability to understand the mechanisms involved in the production of his seizures—then one can pass to the consideration of medicinal or drug therapy.

One of the oldest and most commonly used remedies is alcohol. A small drink of a reasonably strong alcoholic beverage, such as brandy or whisky, by peripheral vasodilatation, we believe, will often relieve the seizure of angina pectoris. Warming of the body relieves angina pectoris. When the patient comes to rest, ceases his exertion, angina pectoris passes rapidly. The dangers of alcohol are the dangers of inducing, possibly, some dependence on the drug, or addiction.

There are other agents which do not give rise to this difficulty. Paramount in importance are the nitrites. Many nitrites are available; some act rapidly, others slowly. One of the earliest used was amyl nitrite, rather an evil smelling, very volatile liquid which is difficult to employ because of its high volatility and must be used in the form of pearls, little glass capsules which are broken by the patient at the time of his seizure. It produces disagreeable secondary symptoms which the patient must endure if he is to use it. They consist of a general sense of discomfort, a wave of warmth over the blush area, a feeling of fullness or of bursting and throbbing in the head, particularly in the temporal region and in the neck. However, amyl nitrite acts within a few moments in the majority of instances, and synchronous with the flushing, sometimes even preceding it, there is a beginning relief of the seizure of pain. Another objection to amyl nitrite is that the pearls frequently break by exposure to ordinary changes in temperature. I have known more than one instance in which a box of amyl nitrite pearls exploded spontaneously after being carried around in a physician's bag for a short period of time. More satisfactory than amyl nitrite is nitroglycerin which is available most conveniently in the form of hypodermic tablets. These should be reasonably fresh because they tend to lose potency either from deterioration or evaporation. The smallest dose which is effective is the dose which should be employed. Many physicians have fallen into the practice of using routinely a dose of $\frac{1}{100}$ gr. or 0.6 mg. This is usually larger than is needed by the patient, and is accompanied by disagreeable side effects, which are closely similar to those that I have just

recounted for amyl nitrite. One can sometimes relieve the attack equally well with one-half of that dose, 0.3 mg., or 1/200 gr., sometimes even with a smaller amount. It is wise to test out the patient's responsiveness and let him use the smallest dose which will give relief. The drug is rapidly absorbed from the buccal mucosa. The tablet should be put into the mouth, chewed but not swallowed. Effects will develop within a few minutes. Relief, if it is obtained, follows promptly and the dosage may be repeated as frequently as necessary. Although relief may be readily obtained in this way, the goal of the physician should be to guide the patient away from unnecessary medication by the previous plan of education. Other nitrites are less serviceable, in my experience, than nitroglycerin. Erythrol tetranitrate, octyl nitrite, sodium nitrite and many others are possessed of reasonably rapid action but slower than nitroglycerin.

If the attack does not pass off within a few minutes after one or two doses of nitrites, doubt concerning the diagnosis of angina should be entertained. They are, therefore, of some, although very limited, diagnostic value.

Nitroglycerin may also be used as a preventive of angina in small doses, 1/200 gr. or 0.3 mg. or thereabouts, taken prior to exposure to factors which previously have precipitated attacks. Knowledge of this action may permit patients to undertake, in emergency, tasks which otherwise would be interrupted by intolerable pain.

I do not know of any other agents that are really effective in the treatment of the seizure of angina pectoris, or that compare favorably with the two that I have mentioned, namely, alcohol and nitroglycerin. We have tried the administration of aminophylline, a dose taken three or four times a day, on the theory of its dilating the coronary arteries. In some patients it seems to diminish the frequency of the attacks. It, however, is by no means trustworthy for this purpose. It has a tendency to make the patient a little bit more alert than usual. It often makes him nervous and should be combined, therefore, in such patients with the administration of a mild sedative, such as phenobarbital in a small dose.

The second type of symptomatology from coronary artery disease is that of myocardial infarction, so frequently miscalled coronary occlusion. Myocardial infarction may occur without coronary occlusion and it is the infarction of the myocardium that is important rather than the occlusion of the coronary artery. The symptoms differ from those of angina pectoris in a few dramatic respects that are easily recognizable and make the diagnosis comparatively simple. In the first place, it is usually spontaneous in its origin. The pain appears without relation to effort or emotional stress or strain, or perhaps I would be more accurate if I said, without necessary relation. It is located in the same areas. It has the same general characteristics, but it does not respond to rest, to alcohol or to nitroglycerin. A precordial pain, or pain in the shoulders or neck, which comes on abruptly and does not respond to these measures, should be thought of as a possible myocardial infarction. If the infarction be minor, there may be few or no other immediate symptoms. The pain and associated symptoms may last for many minutes to several hours if untreated.

With an infarction of the myocardium we are faced with a train of potentialities that may be serious or even fatal. Sudden death may occur while the patient is sitting quietly in his chair or during any degree of activity. There is nothing we can do for this because we do not reach the scene in time, and it is questionable, even if we did, whether treatment would be effective. In the majority of cases the patient makes a partial recovery spontaneously after a brief

period of time, measured usually in hours, sometimes in days. During this early period the patient may show any one of a train of symptoms which demands some medical care. He may go into an early collapse or shock. He may merely complain of nausea and vomiting and break out in a profuse cold sweat. He may have disturbances of his bowel function and of the bladder.

Once the diagnosis is suspected, therapeutic steps should be taken. The patient should be put at complete rest. By "complete rest," we mean no voluntary activities on the part of the patient. This should not be continued for too long a time lest we induce thrombosis in the veins of the lower extremities and complicate the picture. But that does not occur promptly. The most immediate measure is the administration of one of the opiates. Any opiate that is available may be used. I prefer morphine, dilaudid or pantopon, but whatever opiate is present and available should be administered. The dose should be enough to relieve the patient of symptoms. In the case of morphine this is seldom less than 15 mg. and may be two or three times that dose. Corresponding doses are higher in the case of pantopon, lower in the case of dilaudid.

One may then consider the use of other sedatives, or one may turn to the use of oxygen because the embarrassment of the cardiac circulation is very great and these patients often present a picture of relative anoxemia. Oxygen by inhalation often relieves the pain and it diminishes the amount of opiate that is necessary. This should be continued as long as may be needed. The opiates should be replaced, I believe, as soon as possible by other sedatives. The barbiturates are the sedatives of choice. Hydrated chloral may be used, but the barbiturates are usually well borne and are usually quite effective, the idea being to keep the patient at mental and emotional rest during the earlier stages of his convalescence from the acute attack.

If the attack be more severe, the patient may develop symptoms suggestive of pulmonary edema or may actually go into pulmonary edema. This probably is best met, in addition to the use of opiates and oxygen, by the intravenous injection of aminophylline, 0.24 to 0.48 Gm., given slowly, intravenously. By "slowly" I mean within a period of five to ten minutes. This will often relieve the symptoms of pulmonary edema. Atropine in large doses may relieve it, in doses of 2 mg. or thereabouts. If it be very urgent, this may be administered intravenously, or preferably intramuscularly or subcutaneously.

Papaverine has been advocated by a good many. By mouth, in my experience, it has been useless. It must be injected subcutaneously or intravenously to be of any value. Its purpose is relaxation of the vessels. I do not consider it a highly trustworthy or valuable agent in these conditions.

Atropine has recently been hailed as highly effective in coronary thrombosis, aside from its use against pulmonary edema. My own experience with it has been rather unsatisfactory.

Then, there is another picture of myocardial infarction, that in which the patient presents, in addition to those just recounted, symptoms of acute and progressive congestive heart failure. Under these circumstances one must resort to digitalization. I do not think I need to say much about digitalis or its administration if Dr. Gold or others here have talked to you about it. For immediate digitalization we may use either digitoxin, that is digitaline nativelle, or purodigin, or the digitoxin that is now on the market by Squibb, or we may use ouabain, or digitalis leaf, or a liquid preparation of digitalis as conditions demand. For rapid use, however, one of the preparations to be introduced intravenously

is preferable, although under these circumstances I think we must remain a bit cautious in the rapidity with which we digitalize the patient. In a heart that has suffered a more or less extensive and an undetermined degree of myocardial destruction, we may do harm by too rapid digitalization. Probably the wisest procedure, therefore, would be to give digitoxin by mouth, giving a full digitalizing dose of 1.2 mg. according to Dr. Gold, or 1.5 mg. according to my experience. The difference is a minor matter. Give it by mouth and then follow up with a maintenance dose. If we use ouabain, not over 0.5 mg. should be injected initially, and none if the patient has been taking digitalis. But I am assuming that the patient has not. Then the remainder of a dose of 1 mg. total for the first twenty-four hours may be administered in fractions of your own choice, anywhere from 0.1 to 0.2 or 0.3 mg. per fraction.

Measures to combat loss of water and of salt, such as clysis or slow infusions of glucose in water or glucose in physiological saline should be used. Morphine is continued until the patient begins to recover.

DR. GOLD: Dr. Pardee, have you any special points you would like to make before this subject is opened for general discussion?

DR. HAROLD E. B. PARDEE: I would stress one character of the symptomatology which I do not think has been sufficiently emphasized, namely, symptoms of shock. Some of these patients are evidently in shock, almost pulseless, with marked fall of blood pressure, and with other signs associated with shock. In these cases, I think we have to consider one other feature of therapy, and that is, how much we shall attempt to increase the blood volume. The use of intravenous glucose should be considered, either as injection of 50 per cent glucose or as a slow intravenous drip. There is the danger in these cases that, if one gives too much liquid, one may induce cardiac failure. There may be some protection in the falling blood pressure; it can, however, go too far.

DR. GOLD: Dr. Stewart, have you anything to add?

DR. HAROLD J. STEWART: I have very rarely seen a patient who went into shock who did not do very well. As a matter of fact, there have been some observations, which I think were reported to the Society for Experimental Biology and Medicine, in which the patients were put under luminal right after they had coronary occlusion, to the point where they were almost in a state of shock. The patients that I have seen treated for shock *per se* have usually done very badly. If the patients receive extra fluid intravenously or if glucose is given intravenously, fluid is drawn into the blood stream and the extra blood volume may do more harm than good.

So much for that side of it. On the other hand, I very rarely use luminal in a patient who has had acute coronary occlusion because of the lowering of blood pressure which may occur with this drug; consequently, that one sign which you may have to use as evidence of a coronary occlusion, namely, fall in blood pressure, cannot be relied on and you may obscure the diagnosis.

DR. EGGLESTON: May I ask if that type of patient usually requires a sedative in your experience?

DR. STEWART: In the early stages I would prefer the use of morphine or codeine to luminal as a usual procedure.

DR. WALTER MODELL: I would want to know why patients in shock with coronary disease are not given plasma. Perhaps, the reason they do not do so well is that they do not receive plasma but glucose in saline instead.

DR. STEWART: I would not give them plasma for the same reason I would not give them glucose intravenously.

DR. GOLD: Would you give them plasma, Dr. Pardee?

DR. PARDEE: I have not, as a matter of fact, used it but I think it would be good.

DR. GOLD: Would you give it, Dr. Eggleston?

DR. EGGLESTON: I would.

DR. GOLD: How much would you give?

DR. EGGLESTON: Depending upon the patient's response. I doubt if I would go above 300 cc. maximum and probably stay well below that, about 200 cc. I have not had much experience with it because it has not been very readily available and I have had to resort to other measures, chiefly glucose or clysis of glucose. I should have mentioned this. We have to restore the fluid and clysis is safer than intravenous infusion.

DR. GOLD: Dr. Stewart, what would you do in the case of a patient who has had an attack of coronary thrombosis and you see him about four hours later; he has a blood pressure of about 60 and a heart rate of 120; he has extreme thirst; the respiration is depressed and he is cold and clammy?

DR. STEWART: Put him in an oxygen tent and let it go at that so far as treating shock is concerned, I think.

DR. GOLD: It is my experience that patients who have had a coronary thrombosis and are in advanced shock, are apt to do badly, and a high proportion of them fail to survive no matter what treatment they receive. I firmly believe, however, that some of them, who would otherwise succumb, can be saved by the use of plasma. The discussion here reveals the state of general experience with plasma in the shock of coronary thrombosis. Its use in these cases is certainly not very general. I have used it many times; and it is hard to escape the conviction that in occasional cases of severe collapse following a coronary thrombosis, it has supplied the necessary boost to insure recovery. I refer, of course, to cases in which the skin is cold and clammy, the pulse is rapid, the blood pressure is either so low or the pulse so feeble that the pressure cannot be registered with the usual method, or registers by an occasional sound at a level of 60 or 70 mm. mercury. I rarely advise it in the milder cases of circulatory depression following a coronary occlusion in which the blood pressure may decline to a level of around 100 mm. systolic. Most of these patients seem to have a fairly satisfactory circulation. Their skin is warm and the heart beat may be fairly slow. In the vast majority of such cases, the circulation rights itself and plasma may be withheld because, while it may be advantageous, it is not free of dangers. It is easy to overload the heart during the infusion of plasma, in which case the patient is seen to develop respiratory distress and pulmonary râles while plasma is entering the circulation. Judgment is necessary in regard to the dose of plasma. I follow the practice of injecting about 250 cc. in the first hour. If the blood pressure is boosted to levels close to 90 or 100 mm. mercury, the injection is interrupted and the blood pressure taken at frequent intervals. If the pressure resumes its downward course, more plasma is injected, and it is continued in the endeavor to maintain the pressure at a level of at least 90 or 100 mm. mercury, even if it takes a liter or more to do so. This cannot be made a routine procedure and must be kept under the immediate supervision of the physician, for the injection should be interrupted at the first sign of respiratory discomfort, or the development or increase of pulmonary râles. If you set up the infusion and then go off for a time with the expectation that all will go well, you stand a good chance of finding the patient in pulmonary edema when you return. There is no fixed dose of plasma. The proper dose is that which will fill the vessels sufficiently to raise the blood pressure to a safer level, usually around 100 mm. systolic, without inducing pulmonary edema, and the amount that will

keep it there or higher. I am also inclined to suspect that the intravenous infusion of glucose in water or saline in these cases may do more harm than good, for it seems that the fluid passes so quickly into the pulmonary tissues giving rise to edema of the lungs.

DR. CHARLES H. WHEELER: Why do you think these patients go into shock, Dr. Eggleston?

DR. EGGLESTON: The interference with cardiac function gives rise to circulatory changes which result in secondary peripheral vascular failure.

DR. WHEELER: I have always thought of it as largely due to the fact that the cardiac output is substantially reduced. However, I have never been able to understand how administering fluids can help in a person whose heart already cannot do the work that is required of it. What do you hope to gain by treating the shock?

DR. EGGLESTON: The heart output may be improved by supplying more fluid. I believe that the peripheral circulatory collapse is to a considerable extent secondary to loss of fluid caused by the profuse sweating and the nausea and vomiting that occur in these patients.

DR. GOLD: Perhaps a word at this point, about one way in which the mechanism is formulated, may help to tie things together. In coronary thrombosis, it is a fact that the cardiac output falls, the circulation slows down and in one type of reaction the heart is unable to deliver as much blood as it receives. They develop the syndrome of congestive failure. Under such circumstances infusions are likely to make matters worse. In another type of reaction, there are the same initial phenomena, namely, sudden fall in cardiac output and slowing of the circulation. Events then take a different course. The slowing of the circulation may be so pronounced that sufficient anoxia develops to increase seriously the permeability of the capillaries. Fluid passes into the tissue spaces, the blood volume falls and hemoconcentration results. Now the heart fails to receive as much blood as it can deliver even in its weakened state. It starts out as acute forward failure of the heart, but capillary paralysis takes over with a train of self-propagating circulatory changes which soon become irreversible and lead to disaster. The administration of plasma increases the volume of blood and volume of circulation.

DR. WHEELER: May I say something else, Dr. Gold?

DR. GOLD: Yes.

DR. WHEELER: No one has mentioned two factors that are, I think, most important in the treatment of angina. I am sure that most people agree on the importance of convincing the patient with angina that he is not going to drop dead. The term angina has a bad reputation among the laity and much good can be done by reassurance. The second point is to teach them the importance of doing things slowly. It is all very well to tell them to take it easy, to avoid hard work or to refrain from doing this or that. But I think a great deal of this advice misses the mark unless the importance of the speed at which they do things is duly impressed upon them. I think it is a fact that a great many people with angina can do almost anything they wish to, if they do it slowly enough, although they may not be able to walk one block without pain if they do it at a rapid pace.

DR. EGGLESTON: I agree. I tried to include that in the very broad general statements that I made in the beginning, regarding the re-education of the patient, the careful study of the patient and of the factors which precipitate his angina and to eliminate those.

DR. STEWART: There is one more drug that was not mentioned, namely, theobromine and sodium acetate. In Riseman's very well controlled study of the drugs which are useful in taking care of patients

with angina pectoris, it rates high and I think next to nitroglycerin in preventing expected angina after a controlled amount of exercise.

DR. GOLD: How does it rate in your experience, Dr. Pardee?

DR. PARDEE: Very satisfactorily. I personally feel a little more enthusiastic about the theophylline-theobromine type of drugs than Dr. Eggleston indicated. I do not think that the number of patients who show striking changes with these drugs is large, but there are some who certainly do show symptomatic improvement. I, therefore, believe it does something to the heart which is beneficial, which may not in all cases be sufficient to put the symptoms below the threshold of sensation, but which in all cases must have some action.

DR. GOLD: Are you sure it is not simply a placebo?

DR. PARDEE: I do not think it is entirely due to a placebo type of action because of the way patients react. I know that experiments have been performed in which placebos have been given, and it has been concluded by excellent observors that placebos are just as beneficial as the supposedly active drugs. But I have seen things happen which made me think that the drugs are really active. I think that both aminophylline and theobromine and sodium acetate are effective. One cannot decide which is better without a long series of experiments.

DR. STEWART: There is a good paper in a recent issue of the American Heart Journal, by Mokotoff and Katz, which I think gives controlled data relating to this. They show statistically in large series of animals that aminophylline given in amounts comparable to those used in the clinic reduced the size of cardiac infarction in dogs.

DR. GOLD: I agree it is a fine study, and there is indication in it that aminophylline and papaverine may reduce the size of an experimental infarct in the dog. But it is not quite safe to infer from it that such effects are likely to occur in man after the usual oral doses. Mokotoff and Katz gave 15 mg. of aminophylline per Kg. intravenously as the first dose, the equivalent of an intravenous dose of about 1 Gm. for a man, then the same dose twice a day subcutaneously for seven days, then once a day subcutaneously for forty-nine days. These are quite outside the range of doses that are given to humans.

Dr. Travell, have you anything to say about experimental infarction?

DR. JANET TRAVELL: Several years ago we made a study in cats similar to the one you cited in dogs. The size of the infarcts were measured by the blind test by Dr. Gold. In the cat, aminophylline failed to influence the size of the infarct.

DR. GOLD: I should add at this point that in a study we made of 100 patients with the angina of effort in our clinics, only one could distinguish theobromine or aminophylline from sugar of milk or other placebos when both the patient and doctor were kept in the dark at the time regarding the medication. The exception was a man who we learned could distinguish a difference in taste. Before we were able to eliminate that source of error he died of a coronary occlusion, and with that there vanished the possibility of proof in what might have been our single positive case in 100 patients with cardiac pain.

STUDENT: Dr. Gold, I should like to know what is the danger of giving digitalis to one who has suffered a myocardial infarction.

DR. EGGLESTON: There is the fear of rupture of the softened area of the heart or of producing one of the serious arrhythmias, although I personally have never been convinced that I have seen either accident as a result of its use.

INTERNE: Are there reports of occurrences of such accidents? If there are none, I should think that the patient who is going into shock as a result of a myocardial infarction might well be digitalized rapidly.

DR. EGGLESTON: Digitalis would not in any case be used against secondary shock. It might be of value in the primary circulatory depression by improving the contraction of the damaged heart if the possible danger of throwing the heart with its damaged area of muscle into an uncontrollable and possibly fatal disturbance of rhythm, ventricular fibrillation, can be disregarded.

Does that answer your question?

INTERNE: Not quite. You said you never saw it. Have you heard of it?

DR. EGGLESTON: Yes, I have. I might add that it is not usually possible to prove the occurrence of ventricular fibrillation because the termination of life occurs so shortly thereafter that we seldom have an opportunity to establish it definitely by electrocardiographic records.

DR. MCKEEN CATTELL: But ventricular fibrillation is a frequent cause of death in occlusion, is it not?

DR. EGGLESTON: Yes, and probably more so in cases of digitalis poisoning with occlusion.

DR. GOLD: Dr. Stewart, do you fear digitalis in patients with heart failure and coronary thrombosis?

DR. STEWART: Early if you have heart failure in coronary thrombosis you have to use digitalis and I do not think you have much worry about it; late also you do not have much worry about its use. It is certainly somewhere around the seventh or tenth day when necrosis is most marked that there is a real danger of rupture. There has been one instance of rupture here which I believe was due to such a cause. If one watches a patient before and after rapid digitalization, it is possible to distinguish differences in the cardiac contraction. After the drug has been given the beat is forceful, the thrust becomes more marked.

DR. CATTELL: Do you believe that the actual pressure against the infarct is greater after digitalis?

DR. STEWART: I think the force of contraction is much greater and if you have a certain amount of blood in that cavity to force out and you have a weak spot, you might have a blowout.

DR. CATTELL: That would depend on the production of a higher pressure, would it not? You have to assume that the pressure was raised. I am not sure there is proof of that.

DR. EGGLESTON: I do not think I have ever seen a blowout of the ventricle that I thought was due to digitalis.

DR. GOLD: How about you, Dr. Pardee? Did you ever withhold digitalis in a patient with heart failure because a myocardial infarction was there?

DR. PARDEE: I do not give it to patients in shock, but to those with signs of heart failure, I use it in less than the usual doses, because of the experimental work which shows that the heart with infarction is more liable to ventricular fibrillation from digitalis. I use about half of the ordinary dose in such cases.

DR. TRAVELL: Some years ago a study was published from this laboratory which showed that cats take 25 per cent less than the usual fatal dose of digitalis to produce ventricular fibrillation after experimental infarction.

DR. GOLD: I have often wondered about the practical significance of that fact since the safety margin is so large in clinical digitalization.

DR. EGGLESTON: I do not usually use the full digitalizing dose at once in the presence of myocardial infarction.

DR. PARDEE: Granting that there is a safety margin, one might still exceed the limits of safety with the usual dose, if the patient happens to be 25 per cent more susceptible than the average and then has an additional 25 per cent increased susceptibility brought on by the coronary thrombosis. We must be wary because ventricular fibrillation may be fatal.

DR. GOLD: I agree it is a good plan to keep digitalization on the light side in these cases, but it will keep us from exaggerating the danger of digitalis if we remember that nearly double the average digitalizing dose is without serious consequence in the average case of heart failure.

I should like to remind you that the risk of digitalis in myocardial infarction has been considered here only in relation to the danger of cardiac rupture and ventricular fibrillation. Two other possible dangers have recently been pointed out. There are some observations that digitalis shortens the coagulation time of blood. It is denied by others. In the *J. A. M. A.* of August 4, 1945, there is a report by Askey and Neurath in which they fail to find increased blood clotting as a source of trouble, but point to the danger of death from emboli in the systemic circulation dislodged by the increased contraction of the heart. I am not impressed with the evidence for either of these dangers. The paper by Askey and Neurath deals with a group of terminal cases. It clearly shows that old age, long-lasting fibrillation and congestive failure bring about a state in which a high incidence of fatal systemic emboli is encountered, but the groups are not sufficiently large or comparable to establish the rôle of digitalis in dislodging these emboli.

It looks like our time is up. There still remain a number of important issues regarding the treatment of coronary disease which we have not touched. I think it would be well to resume the subject at this point in next week's conference.

SUMMARY

DR. GOLD: Let me now briefly sum up the essential points that were discussed today. It was pointed out that there are several clinical varieties of coronary artery disease, each requiring special attention in treatment. Dr. Eggleston presented a brief outline of the essential aspects of the therapy of this disease. Special attention was paid to the matter of the treatment of shock in acute coronary thrombosis with the use of clyses, glucose infusions and plasma. The view was expressed that attempts at the specific treatment of shock may do more harm than good, while others maintained that infusions, especially of plasma, are in some of these cases a life-saving measure. The rationale was discussed and the dangers were pointed out. Patients with coronary artery disease are often in the state of fear and apprehension arising from the reputation of this disease as a cause of sudden death, and it was urged that all measures possible be taken to reassure them and to point out that they are able to do a great many things if they will only curtail the speed of activities to the limits of their capacity without distress. The eternal question of the purines was explored. There are those who believe that theobromine and sodium acetate is very valuable in the control of the angina of effort, those who believe its action is that of a placebo, and there are the various shades of opinion between these two extremes. The significance of the observation that aminophylline reduces the size of the experimental infarct in dogs was questioned on the grounds that it is apparently not applicable to all species of animals since it does not occur in cats, and on the grounds that the dosage which was used in dogs was so large as to be out of line with the dosage commonly used in man. There was the question of the use of digitalis for the treatment of heart failure which sometimes occurs in patients with coronary thrombosis. The discussion covered the various supposed sources of dangers, ventricular tachycardia, rupture of the heart, increased blood clotting and dislodgment of emboli to the systemic circulation. Not all people are equally impressed with the evidence for any of these dangers when digitalis is employed in proper dosage.

(*To be continued.*)

Case Reports

Isolation of Virulent Treponema pallidum from Human Aorta Thirty-two Hours after Death from Cardiovascular Syphilis*

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GALVESTON, TEXAS

After a comprehensive review of the literature on syphilitic aortitis, Longcope[1] stated in 1913: ". . . . the presence of spirochetes in these lesions, as might be expected, cannot by any means be constantly demonstrated with Levaditi stain. . . That these organisms are *Treponema pallidum* seems almost certain though actual proof of such by culture from the arterial lesions, a most difficult task, or direct inoculation into animals, has not as yet been accomplished."

The above statements hold true today. The demonstration of spirochetes in tissue sections, in spite of recent improvements in staining method, is still a difficult task, while cultivation on artificial media has not been successful. Search of the literature failed to reveal any report on the demonstration of Treponema pallidum by direct inoculation into animals of aortic tissue obtained from human cases.

We believe that the demonstration of the causal relationship between Treponema pallidum and the aortic lesion must in the end rest upon the isolation of viable organisms by animal inoculation.

Recently, a patient in the Peiping Union Medical College Hospital died of cardiovascular syphilis and presented gross changes in the aorta at autopsy. The material obtained from this source was considered suitable for inoculation into rabbits. As the result, virulent Treponema pallidum was isolated from the aortic tissues. This single observation seems worth recording as it is the first time, according to our knowledge, that living treponemes have been shown to be present in the walls of the diseased aorta. Furthermore, the isolation of virulent Treponema pallidum from cadavers, many hours after death of the patient, is of practical importance to the pathologist, from the standpoint of possible infection at the autopsy table even though the infection with syphilis has been of long standing.

CASE REPORT

H. Y. C. (No. H-74404), a Chinese rickshaw puller, forty-six years of age, was admitted to the out-patient clinic on October 21, 1940. His main complaints were pulsations in the abdomen and neck and nocturnal dyspnea. The illness began in February, 1940. Since March, he experienced also a burning and distending pain beneath the upper end of the sternum, together with epigastric pain which was not related to meals.

The dyspnea was paroxysmal in character and the patient had usually two or three attacks each night. In order to relieve the suffocating sensation he had to sit up or walk about. He was usually free from symptoms in the day time.

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From May to August, after taking some Chinese drugs and bed rest, he was practically free from symptoms. He then became a peddler. However, the symptoms returned in September with increased intensity; he became orthopneic and his sleep was disturbed.

Following repeated venereal exposures a genital sore appeared when the patient was twenty-two years of age. For this sore he took several doses of Chinese medicine by mouth in addition to the local medication. He never received injections. Several asymptomatic subcutaneous nodules appeared at both greater trochanteric regions over twenty years ago. Subsequently, he enjoyed good general health up to the time of his present illness.

Examination showed a sick and distressed individual with marked pulsations in the neck. The findings of interest were limited chiefly to the cardiovascular system. The heart was moderately enlarged to the left and the retromanubrial dullness was widened. A systolic thrill was detected over the apex of the heart. There was a loud systolic as well as a diastolic murmur at the base, which was louder in the aortic than in the pulmonic region. At the apex of the heart, a loud systolic murmur and a rumbling diastolic murmur were also audible. Pistol shot sounds, Corrigan's pulse and capillary pulsations were present. The blood pressure was 130/42 mm. of mercury.

Moist râles were heard in the lung bases. The liver and spleen were not palpable. The tendon reflexes of the lower extremities were absent except for the right knee jerk which was elicited with difficulty. The pupils and ocular fundi were normal. Matted subcutaneous, hard, nontender, large nodules, measuring 2 to 5 cm. in diameter, were found over both greater trochanteric and at the sacrococcygeal regions.

The blood serum gave strongly positive reactions to the Wassermann and Kahn tests, but the spinal fluid was entirely normal. Roentgenologic examination showed that the heart was 50 per cent over size and not boot-shaped. The enlargement was chiefly to the left. The pulmonary conus was prominent. The aorta was prominent with suggestive calcification along the ascending and descending portions but without definite dilatation. The subcutaneous nodules were seen as homogeneous soft tissue masses over the greater trochanteric region. The electrocardiogram showed a flat T in lead 1, depressed S-T in leads 2 and 3, slurred R_3, and R_4 averaged about 2 mm. in height—findings suggesting myocardial damage and coronary insufficiency. There was no axis deviation. The circulation time was 19 seconds by the saccharine method. The blood picture was one of mild anemia. The urine was normal and the phenolsulfonphthalein excretion was 55 per cent at the end of two hours.

The above history and findings led to the diagnoses of cardiovascular syphilis with aortic insufficiency, narrowing of coronary ostia, cardiac enlargement and failure, syphilitic juxta-articular nodules, and questionable syphilis of the central nervous system.

Digitalization resulted in some improvement in the cardiac condition, though slowly. The patient was admitted to the ward on November 13th where there was considerable improvement in his condition following bed rest and the administration of digitalis, potassium iodide and hypertonic glucose solution. After a month's stay he was discharged from the hospital with instructions to have further rest and to continue digitalis. Perhaps because he failed to carry out the instructions, his condition became worse.

When again admitted to the ward on February 15, 1941, the patient was found to be very sick, with orthopnea, marked pulsations in the neck, cold sweats and Cheyne-Stokes respiration. In addition to the findings noted on the previous admission, the liver was 5 to 7 cm. below the costal margin, and the genitalia and the lower extremities were slightly swollen. He died eighteen hours later.

Autopsy Findings. The corpse had been kept in the ice-chest for twenty-eight hours before the autopsy (No. A3426) was performed. The findings of interest were limited chiefly to the cardiovascular system and the subcutaneous tissue.

The heart (Fig. 1) weighed 740 Gm. and was hypertrophied and dilated. The hypertrophy was particularly noticable in the left ventricle. There was diffuse thickening of the aortic cusps. The anterior and posterior right cusps were

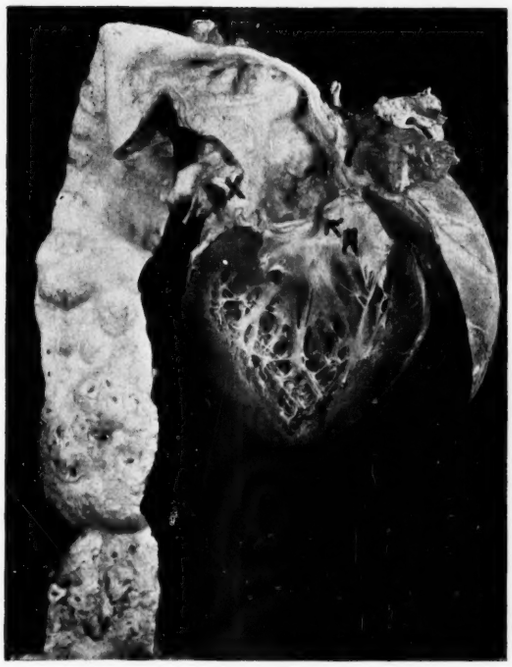

FIG. 1. *Note the hypertrophied wall and dilated chamber of the left ventricle, the thickened aortic cusps, the gaping of the aortic commissure* (A), *and the fusion of the anterior and posterior right cusps. The aorta shows both syphilitic and arteriosclerotic patches.*

fused together while the two posterior cusps gaped a little at their angles. The free margin of each cusp was thickened, round and rigid.

A longitudinal cut of the rigid margin of the aortic cusp revealed a central yellowish area surrounded by a zone of whitish glistening fibrous tissue. Microscopical examination showed that the yellowish area was composed of necrotic tissue, containing degenerated leucocytes and plasma cells. (Fig. 2.) No spirochetes could be demonstrated in the sections.

The mitral valve showed moderate diffuse thickening with two whitish patches on the anterior cusp but there was no vegetation. The tricuspid and pulmonary valves appeared to be normal.

The orifice of the right coronary artery was completely occluded while that of the left was narrowed. The coronary arteries showed very slight atheromatous change.

The aorta was moderately dilated in its entire length. Its intima presented multiple, large and small, elevated, hyalinized, grayish and yellow patches over the entire length of the aorta (Fig. 1), but especially numerous in the ascending arch and in the lower abdominal portion. Some of these patches showed ulceration or calcification. In between these patches, longitudinal shallow and deep furrows, characteristic of syphilitic infection, were observed.

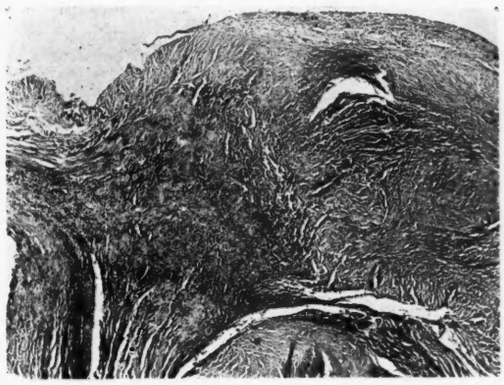

FIG. 2. *Low power view of aortic valve. Note marked fibrosis, lymphocytic infiltration and necrosis.* × 44.

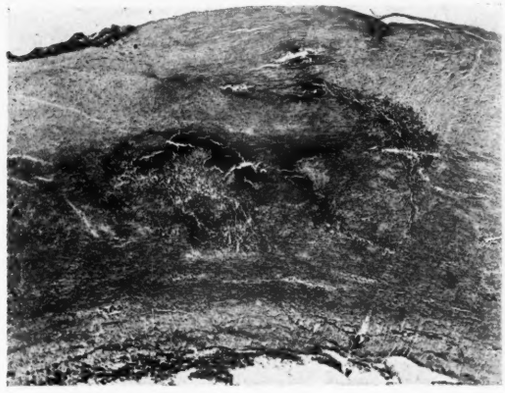

FIG. 3. *Low power view of aortic wall. Note extensive scarring and necrosis (dark areas) of intima and media with perivascular lymphocytic infiltration in media and adventitia.* × 35.

Under the microscope, the intima was found to be much thickened with marked fibrous tissue proliferation. The media contained numerous irregular scars, foci of lymphocytic infiltration, and areas of necrosis which sometimes extended into the intima. (Fig. 3.) Spirochetes were not found in the sections stained by the Levaditi method.

On gross inspection, the subcutaneous nodules were grayish, firm and without definite capsule; the cut surface was glistening and whitish. Microscopically, they consisted of dense, hyalinized, fibrous tissue together with multiple foci of lymphocytic infiltration. The capillaries were congested and there was appreciable peri-

vascular lymphocytic and plasma cell infiltration. No spirochetes were found in the sections stained by the Levaditi method.

ANIMAL INOCULATION

Aorta and Aortic Valve. A piece of tissue measuring 3.5 by 1.0 cm. was removed from the anterior aortic cusp and the adjacent aortic wall. (X, Fig. 1.) For the purpose of sterilization of the surface tissue, the specimen was immersed in 80 per cent ethyl alcohol for three minutes followed by thorough washing (five times) in sterile physiological saline. Then the material was cut into small pieces and ground in physiological saline. Two cc. of this emulsion was injected into the right testis while the remainder (0.5 cc.) was injected into the left scrotal sac of the same rabbit* on February 17, 1941.

Fifty-three days after the inoculation the right testis was somewhat full and felt indurated. The induration increased during the subsequent week. A moderate orchitis had developed by the next week. The material aseptically aspirated from this testis contained actively motile Treponemata pallida, as seen under the darkfield microscope. The left scrotal sac never showed any change.

Mitral Valve. A piece of tissue measuring 1.5 by 1.0 cm. was obtained from the mitral valve, for inoculation into the rabbit, on February 17, 1941. It was sterilized in exactly the same way as was the aortic tissue. The entire saline emulsion (2 cc.) was divided equally and injected into the testes of one rabbit. In the subsequent eighty-eight days, no change could be detected in the testicles. The testicles and popliteal lymph nodes of this animal were transferred into a second series of two rabbits. The latter animals also failed to show any sign of syphilis in an observation period of 111 days.

* The animal was a cryptorchid.

Juxta-articular Node. One of the subcutaneous nodules of the trochanteric region was removed at biopsy. It was finely emulsified in sterile physiological saline, and 1 cc. of the emulsion was injected into each testicle of two rabbits on November 30, 1940. Neither animal showed any clinical evidence of syphilis. On March 27, 1941, both animals were killed and their testicles and popliteal lymph nodes were transferred into the testes of a second series of two rabbits. One of these died of diarrhea two months later without showing any sign of syphilis. The second animal developed a small nodule in the right testis ninety-seven days after inoculation. Under the darkfield microscope, motile Treponemata pallida were found in the emulsion of the nodule.

Fresh Blood. One cc. of fresh circulating blood of the patient was injected, immediately after withdrawal, into each testis of two rabbits on November 30, 1940. No evidence of syphilis developed during the following four months. Transfers of the testicles and popliteal lymph nodes into a second series of two rabbits also failed to produce syphilitic infection in an observation period of ninety-seven days.

COMMENTS

It is quite possible that other workers have made attempts to demonstrate Treponema pallidum in the aorta by the biological method as reported here. However, we have failed to find any positive result being recorded in the literature. We must attribute the success met with in our case to the combination of a number of favorable circumstances.

First, the patient never received any specific antisyphilitic treatment. Even small amounts of arsenical drugs might have led to a negative result. Cardiovascular syphilis, even in the advanced stage, is usually treated with bismuth and arsenical preparations. But, our patient was critically ill on

admission. When his condition improved to the extent that he could be given antisyphilitic treatment (as was actually advised) he left the hospital. He died eighteen hours after the second admission to the ward before any specific treatment could be given.

Secondly, the lesions in the aorta as found at autopsy were very extensive and active. The necrosis in the aortic wall (Fig. 3) was remarkable. Such lesions would more likely contain Treponema pallidum than the older and less active ones.

Thirdly, the time interval between the death of the patient and the inoculation of the aortic tissue into rabbits was not too long for the recovery of viable Treponema pallidum. The tissues were injected into the rabbits thirty-two hours after the death of the patient. The body had been in ice-chest temperature (about 7°C.) for twenty-eight hours and the aortic tissue in room temperature (about 20°C.) for four hours. According to Rosahn,[2] Treponema pallidum in tissues refrigerated for as long as a week should be regarded as infectious.

Taylor,[3] Hoffmann[4] and others have reported accidental innocent infections contracted while performing autopsy. The possibility of infection at the autopsy table should not be overlooked, even though the patient's infection with syphilis has been of long standing. In the present case, virulent Treponemata pallida were recovered twenty-five years after syphilitic infection.

The negative result with the inoculation of the blood is of significance. In the absence of any demonstrable spirochetemia, it is reasonable to surmise that the positive results obtained with inoculations of materials from the aorta and from the subcutaneous nodule meant the presence of viable Treponema pallidum in these tissues. The syphilitic nature of the so-called juxta-articular nodes has been discussed elsewhere.[5] The failure to demonstrate Treponema pallidum in the mitral valve is not surprising, since it is well known that the mitral valve is rarely, if ever, attacked by the syphilitic virus. The anatomical changes found in the mitral valve might well have been the result of an old rheumatic infection.

In the case reported here, careful search has been made by more than one individual for Treponema pallidum in the Levaditi-stained sections of the aorta, aortic valve, mitral valve, heart muscle and the subcutaneous nodule. But, none could be found. However, by inoculation of the materials into the rabbits, viable Treponema pallidum was isolated from the aortic tissue and also from the subcutaneous nodule. Without entering into the debatable question of granular forms of Treponema pallidum, both staining and biological methods depend for success, in a large measure, upon the number of Treponema pallidum present in the tissue. In our case, the number of Treponema pallidum seemed to be too small to allow detection in sections, but it was large enough to insure a positive culture in the testes of rabbits. The superiority of the biological method over the staining method is impressively demonstrated.

Morgan[6] thinks that the number of the organism of syphilis inoculated into a testis of the rabbit should exceed twenty-five (usually over 100) before a positive result is obtained, and that in general the incubation period varies indirectly with the number of the organisms introduced. According to the latter assumption, it seemed that in our patient the aortic tissue contained more Treponemata pallida than did the subcutaneous nodule. The positive result from the subcutaneous nodule required not only longer incubation period but also an extra transfer of tissues to a second series of rabbits.

The venereal history indicated that the patient had contracted syphilis some twenty-five years before his death. The signs of

cardiovascular syphilis lasted about a year. In the intervening twenty-four years the disease was apparently latent.

SUMMARY

Virulent Treponema pallidum was isolated from the aortic tissue of a patient who died of syphilitic aortitis with aortic regurgitation. The aortic tissue was transferred into the rabbit thirty-two hours after the death of the patient. Viable Treponema pallidum was also isolated from the juxta-articular nodules, but not from the circulating blood nor from the mitral valve tissue. The patient died twenty-five years after acquiring syphilis, without ever receiving specific antisyphilitic treatment.

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Acute Monocytic Leukemia*

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RECOVERY from a fulminating leukemic state is sufficiently uncommon to warrant reflection upon any instance which suggests such an event. Accordingly, when in the fall of 1941 a patient whom we considered to have acute monocytic leukemia made an unusual recovery we were inclined to report the case. This was deferred by our anticipation that a relapse would ensue and by the war with the departure of one of us to military duty. Now that the patient has remained well for four and a half years we present the following report.

CASE REPORT

This fifty-year old white man entered the Jewish Hospital on November 17, 1941. He had been known to one of us (H. B. W.) for many years through minor illnesses. A periodic examination in December, 1940, revealed no abnormalities, the hemoglobin and erythrocyte counts being normal. The leucocyte count was 3,500, with polymorphonuclears 70 per cent, lymphocytes 26 per cent, monocytes 3 per cent, eosinophils 1 per cent. On July 21, 1941, a mild anemia was noted, erythrocytes 3.8 million, hemoglobin 84 per cent. The white blood cells were 4,350, with polymorphonuclears 60 per cent, lymphocytes 34 per cent, monocytes 3 per cent, eosinophils 3 per cent.

During the first week of November, 1941, he noticed soreness of his mouth and several days later visited his dentist* for local treatment. Because of a temperature elevation and continuing soreness of his gums he was examined on November 15, 1941, when it was noted that his temperature was 101°F., that there were ulcerating lesions in the buccal mucosa and a small tender lymph node at the angle of the right jaw. The erythrocyte count was 3.6 mil., hemoglobin 84 per cent, leucocyte count 4,900, with polymorphonuclears 22 per cent, the remainder being abnormal.

On November 17th, when admitted to the Jewish Hospital, his complaints were extreme weakness, fever and increasing soreness of the mouth. The skin and mucous membranes were pale. There were ulcerating erythematous lesions in the buccal mucous membranes of both cheeks, more marked on the left where edema of the face existed. The node at the angle of the right jaw was enlarged, otherwise there were no enlarged lymph nodes. The spleen was palpable two finger-breadths below the left costal margin. The liver was not palpable.

On November 18, 1941, the peripheral blood and sternal bone marrow was examined by one of us (H. S. S.) with the following findings: Peripheral Blood: erythrocytes, 2.8 million; hemoglobin, 10.5 Gm.; reticulocytes, 2.5 per cent; platelets, 288,400 (Dameshek's. normal 450,000–850,000); white blood cells, 5900; differential count: monoblasts, 84 per cent; lymphocytes, 16 per cent. The red blood cells were of normal size and shape. No nucleated red blood cells were seen. The platelets appeared fewer than normal. Sternal Bone Marrow: A satisfactory specimen was obtained by aspiration of the body of the sternum. (Figs. 1 and 2.) This was examined with supra-vital and Wright-Giemsa stains. It was apparent that the usual bone marrow elements were replaced uniformly by an abnormal cell. Megakaryocytes were extremely scarce, two being seen on the entire film. Nucleated red cells were very rare, as were granulocytes. An occasional erythroblast and

* Dr. Carlos H. Schott cooperated in the care of this patient.

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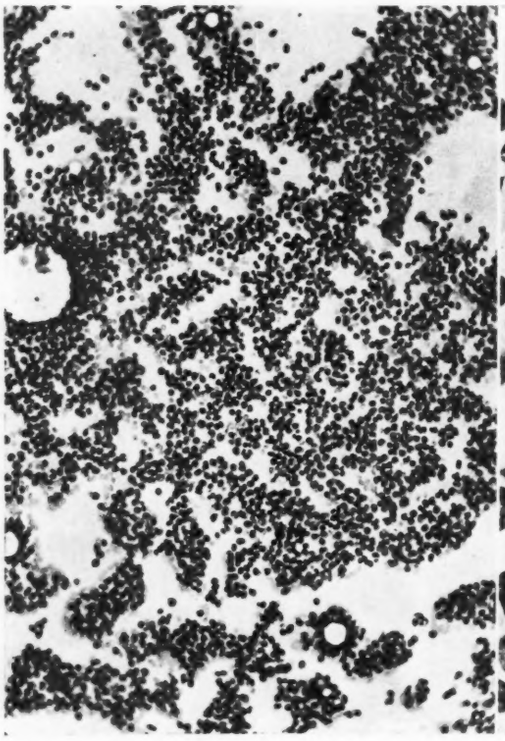

FIG. 1. *Sternal bone marrow smear. Low power, magnification* 30 ×, *demonstrating an infiltration of the marrow uniformly by an abnormal cell. The absence of megakaryocytes is noteworthy.*

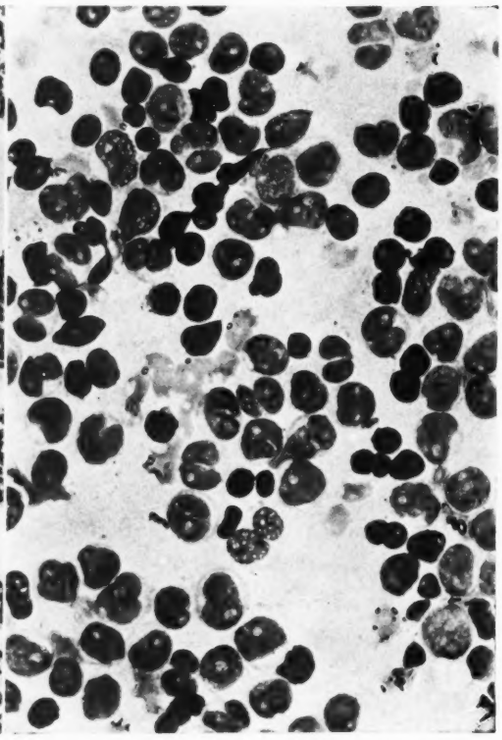

FIG. 2. *Same as Figure* 1 *with magnification* 900 ×. *The characteristics of the abnormal cells are apparent.*

myelocyte were seen. The abnormal cells which made up the substance of the bone marrow appeared "blastic" in type. The nuclei were horse-shoe shaped, indented or double. One to two nucleoli were present. On supra-vital stain many cells had a small collection of neutral red granules in the bend of the horse-shoe, similar to those seen in young monocytes.

This patient was in the hospital 107 days. During the first forty days he was acutely ill. The temperature was a septic type with wide daily swings. (Fig. 3.) He was extremely weak and drowsy. His appetite was very poor and he could swallow only with difficulty. The edema of the face developed into a true noma with spontaneous rupture through the skin. (Fig. 4.) This abscess was opened more fully surgically on December 24, 1941, by Dr. J. Louis Ransahoff. Culture revealed a mixed flora. After this procedure the temperature gradually subsided, the lesion on the face slowly healed (Fig. 5) and his general condition improved. The slow steady progress was temporarily interrupted in the twelfth week by the development of a left parotitis. This was drained on February 12, 1942, and then treated locally with sulfathiazole packs. A rapid fall in temperature occurred after drainage of the parotitis and the use of sulfadiazine orally, but healing was slow and was followed by a partial left peripheral seventh-cranial nerve paralysis. He was discharged from the hospital on March 3, 1942.

The white blood cells, which on admission were around 5,000, rose on the fourth hospital day to 35,000 and for the next forty days ranged between 25,000 and 40,000. This increase in the white cells was comprised essentially of abnormal monocytes. (Fig. 3.) After the fiftieth day the total white blood cell count was within the normal range and remained so except for a two-week period toward the end of the hospitalization when a secondary leucocytosis developed. This was associated with the appearance of the parotitis described above and the cellular reaction was polymorphonuclear.

Frequent observations have been made during

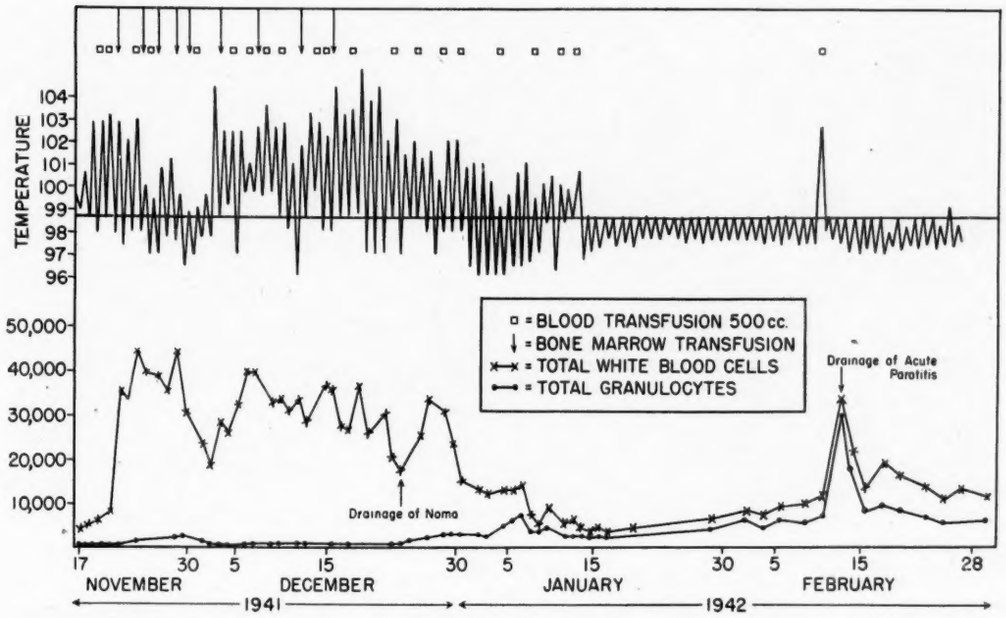

FIG. 3. *Graphic representation of temperature, total white blood cells and total granulocytes during hospitalization. The blood and bone marrow transfusions, and the surgical procedures are indicated.*

this four-year period, March, 1942, to July, 1946. The patient gradually regained his strength and weight. Residuals of the seventh-nerve palsy persist. A blood count on April 23, 1946, was as follows: Erythrocytes, 5.15 million; hemoglobin 15.7 Gm.; white blood cells, 5850; polymorphonuclears, 47 per cent; lymphocytes, 44 per cent; monocytes, 7 per cent; eosinophils, 1 per cent; basophils, 1 per cent. The present appearance of his face is seen in Figure 6.

The nursing care in this case can be described only as superb, and is mentioned particularly because we believe it contributed greatly to the recovery. In spite of high fever, anorexia, dysphagia and great discomfort, considerable nourishment was obtained. An adequate fluid balance was maintained by oral and parenteral routes. Twenty blood transfusions were given in the first sixty days. The oral lesions were treated locally by frequent saline irrigations and by gentle removal of dead tissue, by moist heat to the face, and later by surgical drainage through the cheek, followed by sulfathiazole ointment dressings. Sulfathiazole and sulfadiazine were given orally from February 12, 1942, throughout the remainder of the hospital stay. Nine intrasternal transfusions of sternal bone marrow, each of from 3 to 5 cc., from young healthy donors were given. The secondary parotitis was treated by incision and drainage, subsequent sulfapacks and sulfathiazole and sulfadiazine orally.

COMMENT

Whenever one suggests that a patient with acute leukemia has recovered, whether this recovery be defined as a cure or as a remission, he is immediately subjected to the criticism that the patient did not have leukemia. We recognize that this is a natural and sound attitude and we have re-examined our patient in this light.

Clinical conditions which bear more or less resemblance to the case under discussion are infectious monocucleosis, agranulocytosis, leukemoid states and leukemia. Unlike infectious mononucleosis was the presence of anemia without blood loss, absence of lymphadenopathy, and a negative heterophile agglutination. Unlike agranulocytosis may be cited again the anemia, the absence in the history of any of the known agents which produce agranulocytosis and the presence in the peripheral blood and bone marrow of an abnormal cell. The term

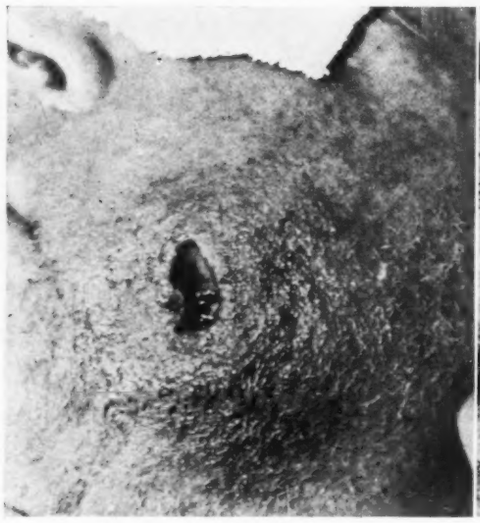

FIG. 4. *Demonstrating the noma, resulting from spontaneous erosion through the cheek of the lesion in the oral mucous membrane.*

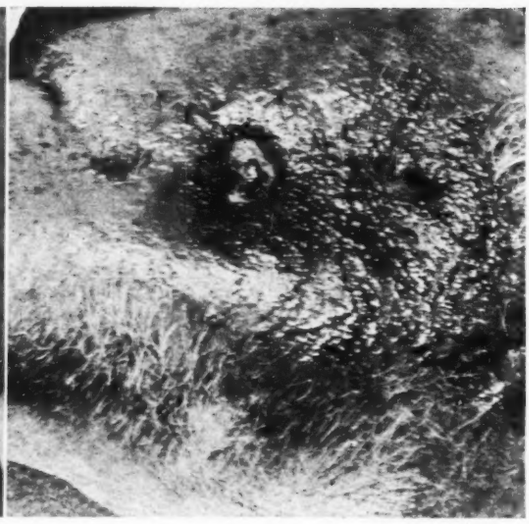

FIG. 5. *Showing healing of the erosion in Figure* 4.

leukemoid has been given to conditions in which large numbers of immature cells, usually of the myeloid series, are found in the peripheral blood associated not with leukemic infiltration of the bone marrow and other internal organs, but with extreme sepsis, with the bone marrow crises of hemolytic anemias, in whooping cough or in metastatic lesions of the bone marrow. Craver[1] states that "in this borderline zone occur the apparent recoveries from leukemia, and it is usual to say that if recovery occurs the disease could not have been leukemia. However, there would seem to be room for speculation as to whether leukemia may not in its early stage be a reversible process and in some cases it is most difficult to decide whether to call the process true leukemia."

The onset of the disease in our case with oral symptoms which sent our patient first to his dentist is characteristic of monocytic leukemia in the experience of Forkner.[2] The progression of oral infection to the state of noma is seen in leukemia (Kracke[3].) The anemia and splenic enlargement are additional features. The platelet count of over 200,000 will be considered not in keeping with an acute leukemia. By the method used we consider this a definite thrombocytopenia though it still is higher than many instances of acute leukemia. Finally, the diagnosis of leukemia depends upon the demonstration of leukemic cells in the peripheral blood, bone marrow or by infiltration into other organs. The peripheral blood and bone marrow were examined on innumerable occasions and our diagnosis rests upon the bone marrow invasion by abnormal monocytic cells (Figs. 1 and 2) which also were present as indicated in Figure 3 in the peripheral blood. In the first weeks of the disease the clinical and hematologic picture indicated an ominous prognosis and this was concurred in by Dr. Raphael Isaacs who saw this patient with us.

Since the etiology of leukemia is unknown, any explanation for recovery in a given case becomes a matter of speculation. However, there are certain clinical similarities between the natural course of events in acute leukemia, in acute agranulocytosis and in acute aplastic anemia. These similarities are seen in the manifestations of sepsis. It is now generally held that the absence of

granulocytes in acute agranulocytosis permits the rapid development of sepsis and accounts for the fatal outcome in many of these cases. Accordingly we postulate that death in acute leukemia may be due not to the presence of abnormal cells but to the *absence of normal cells*. In acute leukemia the disruption of the bone marrow and subsequently of the peripheral blood may be caused by some agent whose action is less permanent than has been usually assumed. It is conceivable that if the body defenses could be tided over such an insult long enough, normal bone marrow function could be resumed and recovery result.

Accordingly, it is our speculation in this case, that an early diagnosis, unusually efficient nursing care, general supportive measures, many blood transfusions, and chemotherapeutic and surgical attack on the oral infection were effective in maintaining the body defenses until the bone marrow recovered from the insult which produced that cellular reaction we call leukemia. The report of Kugel and Schnitker[4] of the control of severe granulocytopenia in a case of aleukemic leukemia by the use of penicillin gives support to the concept that the course of this disease may be modified favorably by agents which control sepsis, even though in their case death was the final outcome.

Mention should be made of the use of sternal bone marrow transfusions. Because the prognosis seemed ominous at the outset of our treatment it was thought advisable on the recommendation of Dr. Raphael Isaacs to give transfusions of small amounts of bone marrow aspirated from young healthy donors directly into the sternal marrow of the patient. This procedure had been recommended earlier by Morrison and Samwick.[5] It was not anticipated that this or any other measure would alter the course of the disease. With the recovery of our patient it becomes necessary to evaluate this procedure. We have tried this method

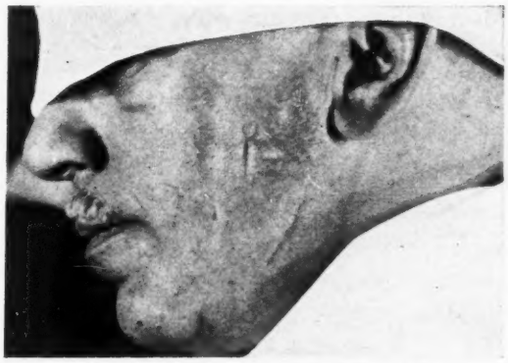

FIG. 6. *The appearance of the face at the present time. The scars of the noma and the secondary parotitis can be seen.*

of treatment in four other patients, two with acute monocytic leukemia and two with acute myelogenous leukemia without success. It is only fair to mention that these patients were all seen late in the course of their disease, and perhaps they did not receive as intensive treatment as the present case. One may still speculate that normal human bone marrow contains something which is necessary for the normal development of white blood cells and that this substance is lacking in acute leukemia. Further use of bone marrow transfusions of bone marrow will be necessary to determine its value in the treatment of acute leukemia.

The prognosis in acute leukemia has been so poor that an attitude of hopelessness has naturally developed, as a result of which often no attempt is made along therapeutic lines. With large pools of blood readily available now, and with chemotherapeutic agents, such as sulfa drugs, penicillin and other antibiotics to combat infection, it is to be hoped that more instances of recovery will be noted. The prospects for such recovery depend, at the moment and until more is known about the etiology of the disease, first upon an early and accurate diagnosis, and second, upon an attitude of optimism which is translated into an active and intensive attempt to prevent the complications of the disease, i.e., sepsis and hemorrhage.

CONCLUSIONS

1. A case of acute monocytic leukemia with noma is reported.

2. The patient has been clinically well and the peripheral blood and bone marrow normal for over four years.

3. Treatment consisted of symptomatic care, many blood transfusions, (twenty in sixty days), chemotherapeutic and surgical attack on complicating infections, and nine transfusions of normal sternal bone marrow during the height of the disease.

4. It is suggested that monocytic leukemia may not be as universally fatal as previous experience has indicated.

5. Early diagnosis and intensive treatment directed to prevent the complications of the disease may confirm this statement.

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5. Morrison, M. and Samwick, A. A. Intramedularry (sternal) transfusion of human bone marrow. *J. A. M. A.*, 115: 1708, 1940.

Editorial

Mechanisms of Edema Formation

REGULATION of the water balance of the body and of the distribution of fluids within the body involves mechanisms which investigations of recent years have disclosed to be more complex than was previously supposed. The results of some of these studies have been summarized recently in two lucid and informative reviews.[1,2]

Water normally constitutes about 70 per cent of the adult body weight and this proportion ordinarily is maintained with remarkable efficiency by a balance between total water intake and output. Of the average daily total intake of 2,400 Gm. of water, about half is taken as water or other beverage, 900 Gm. as preformed water of food and 300 Gm. is water of oxidation formed in the body during the metabolism of foodstuffs. Of the average daily total output, about 1,300 Gm. of water are excreted in the urine, 200 Gm. in the stools and 900 Gm. are lost through the skin and lungs ("insensible loss"). It will be noted that a large proportion both of the water taken in and excreted is not readily measurable by ordinary methods and is not considered in the common bedside practice of estimating water balance by comparison of urinary output with fluid intake. Sunderman points out the fallaciousness of such comparisons, which so often give discrepant results even if apparently complete twenty-four hour urine specimens have been collected. Daily measurement of the body weight usually gives a more satisfactory approximation of gross positive or negative fluctuations in water balance.

[1] SUNDERMAN, F. W. Approaches to the study of edema and dehydration. *Am. J. Clin. Path.*, 16: 353, 1946.

[2] ABBOTT, W. E. A review of the present concepts of fluid balance. *Am. J. M. Sc.*, 211: 232, 1946.

The body water may be regarded conveniently as divided into an intracellular component comprising about 45 per cent of the body weight, and extracellular components comprising about 25 per cent of the body weight. Of the extracellular portion, about 80 per cent normally is found in the interstitial fluids and 20 per cent is contained within the walls of the vascular bed. The interstitial and the intravascular fluids are in dynamic equilibrium, with a constant interchange of water, electrolytes and non-electrolytes across the capillary membrane. In edema, the regulation of this equilibrium is disturbed and an excessive amount of fluid accumulates in the intercellular spaces.

Sunderman has divided the various causes of edema into the following categories: (A) primary retention of water (water intoxication); (B) primary retention of salt (as in overadministration of salt, adrenal cortical and gonadal hormones); (C) reduction of colloid osmotic pressure (hypoproteinemia) due to inadequate protein intake, impaired synthesis of serum albumin or excessive loss of proteins through the kidney or other channels; (D) general or local increases in capillary blood pressure (congestive cardiac failure or mechanical obstruction to veins); (E) blockage of lymphatic return of protein-containing tissue fluid.

Investigation of the mechanisms of edema has resolved itself largely into analysis of the factors influencing the exchange of water, electrolytes and non-electrolytes across the capillary wall and of those regulating glomerular filtration and tubular reabsorption of water. The hydrostatic pressure within the capillary bed and the permeability of the capillary membrane are impor-

tant factors in the movement of fluid from vascular channels into the interstitial spaces. The colloid osmotic pressure of serum albumin and the tissue tension of subcutaneous elastic tissue are the most significant forces in maintaining fluid within the confines of the capillary bed.

Starling's concept of a simple equilibrium between hydrostatic and colloid osmotic pressures effecting a filtration balance at the capillary wall has been borne out, in general, by clinical investigation and animal experiment. The recent work of Keys and his associates,[3] however, has disclosed discrepancies in this relation. In a study of famine edema, which reappeared on a large scale in World War II, Keys placed thirty-four volunteers for six months on a semi-starvation diet of whole cereals, potatoes, turnips, etc., providing an average of 49 Gm. of protein daily. The subjects developed typical famine edema resembling that observed in certain war areas. They lost an average of one-fourth of their body weight and became "waterlogged," with a relative excess of sixteen pounds of extracellular water per man. Like the victims of starvation abroad, the experimental subjects also showed marked polyuria, bradycardia and diminution of heart size, no hepatomegaly and no rise in plasma nonprotein nitrogen or chloride. In accord with previous observations, there was no indication that edema was due to renal or cardiac failure, the venous pressure, in fact, being reduced. Thiamine deficiency was ruled out by analyses of food and excreta.

An unexpected result of this study, however, was the finding that, contrary to earlier observations, the development of edema was accompanied by only a slight decline in the concentration of plasma proteins, averaging 0.73 Gm. per 100 cc., and by no marked hypoalbuminemia. The slight degree of hypoproteinemia or lowered colloid osmotic pressure in the plasma observed clearly could not account for the appearance of marked edema. The discrepancy was all the more striking because it was noted consistently in the subjects of this carefully controlled experiment.

Keys interpreted his data to indicate that the fluid balance between blood plasma and interstitial fluid does not reflect a simple equilibrium of the kind generally postulated. He concludes that there is a dynamic non-equilibrium state of the capillary wall and implies transfer activities of the lining endothelium which have yet to be clarified.

A. B. G.

[3] Keys, A., Taylor, H. L., Nickelsen, O. and Henschel, A. Famine edema and the mechanism of its formation. *Science*, 103: 669, 1946.

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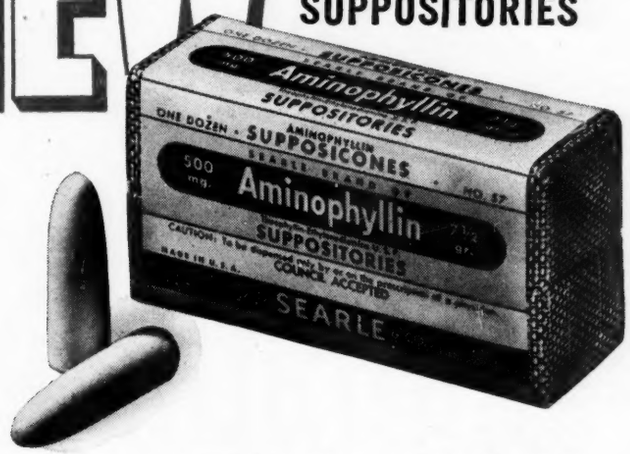

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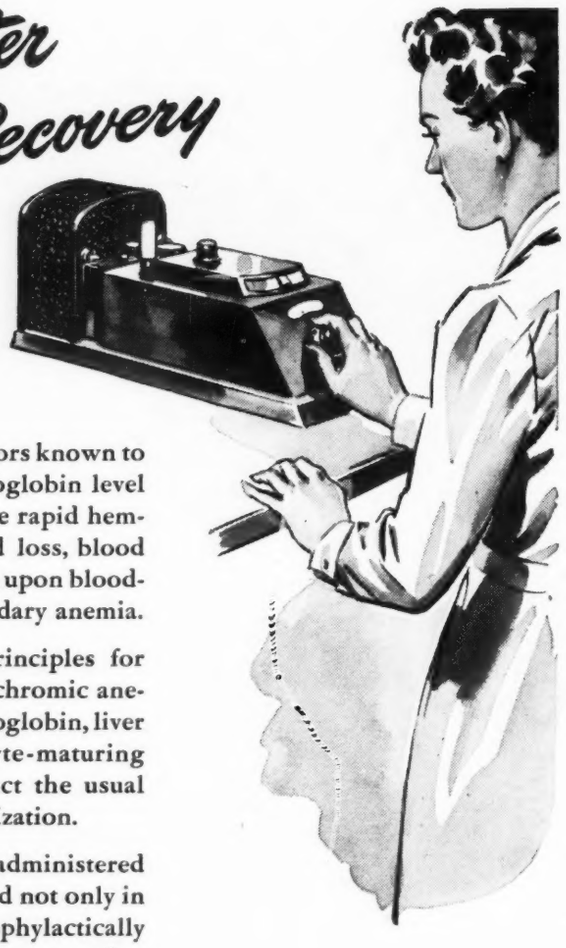

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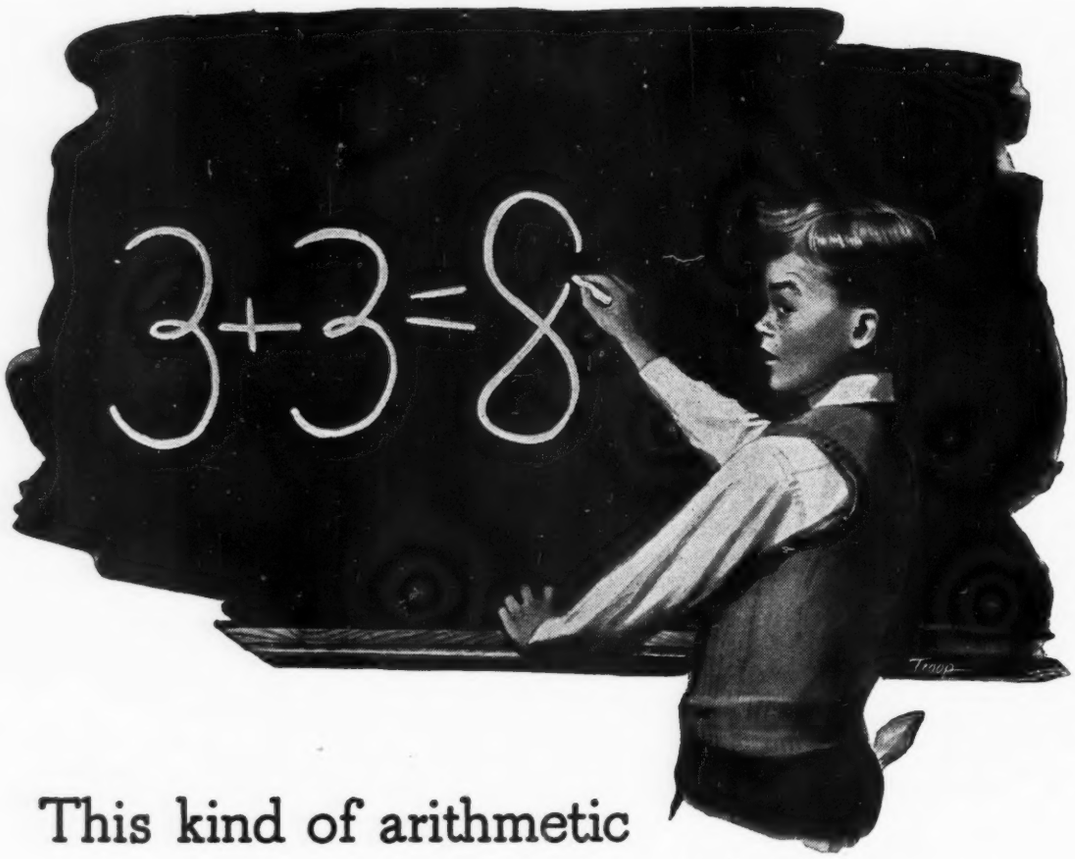

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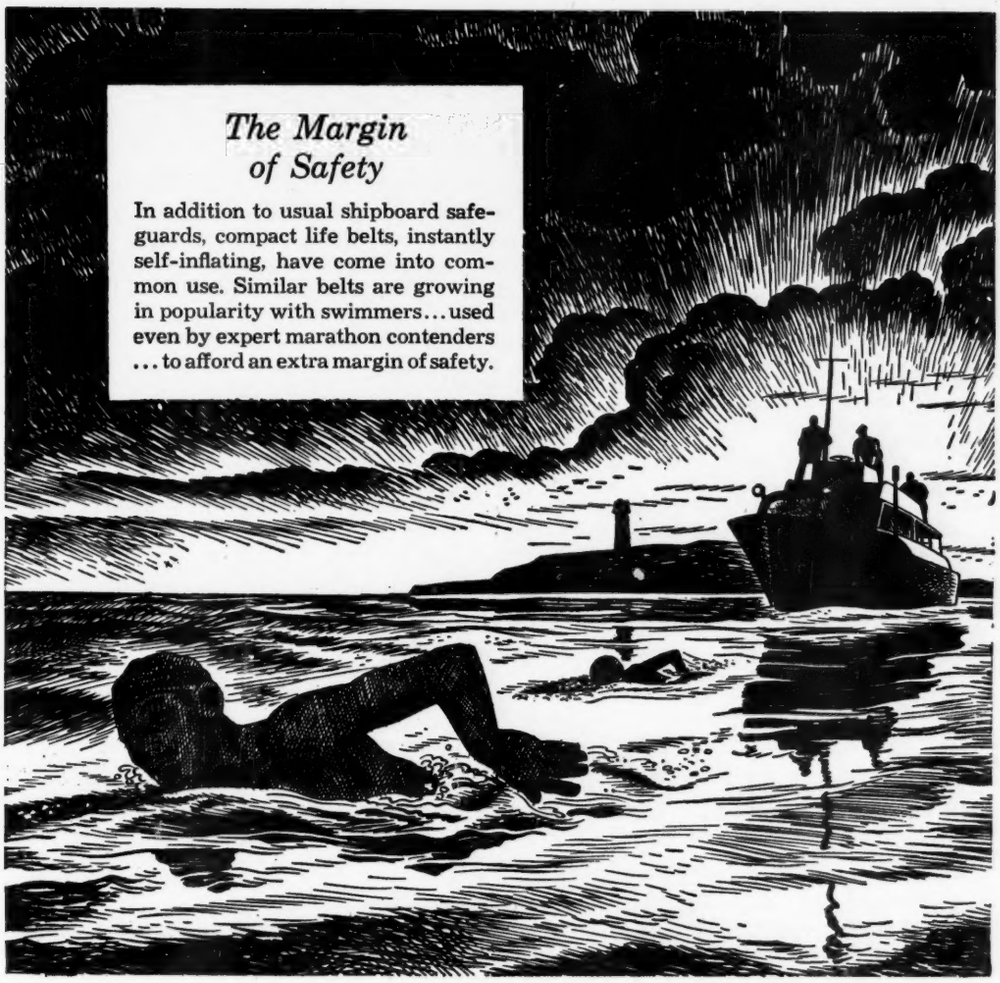

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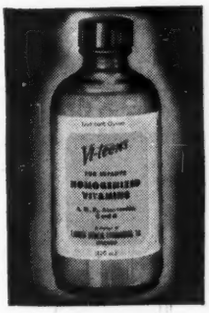

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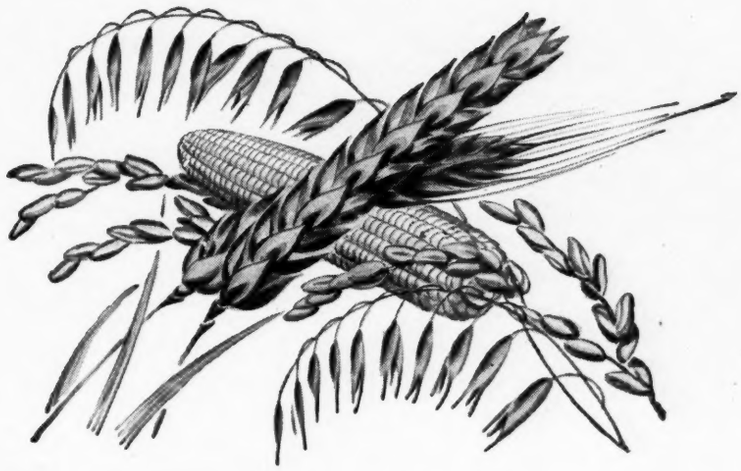

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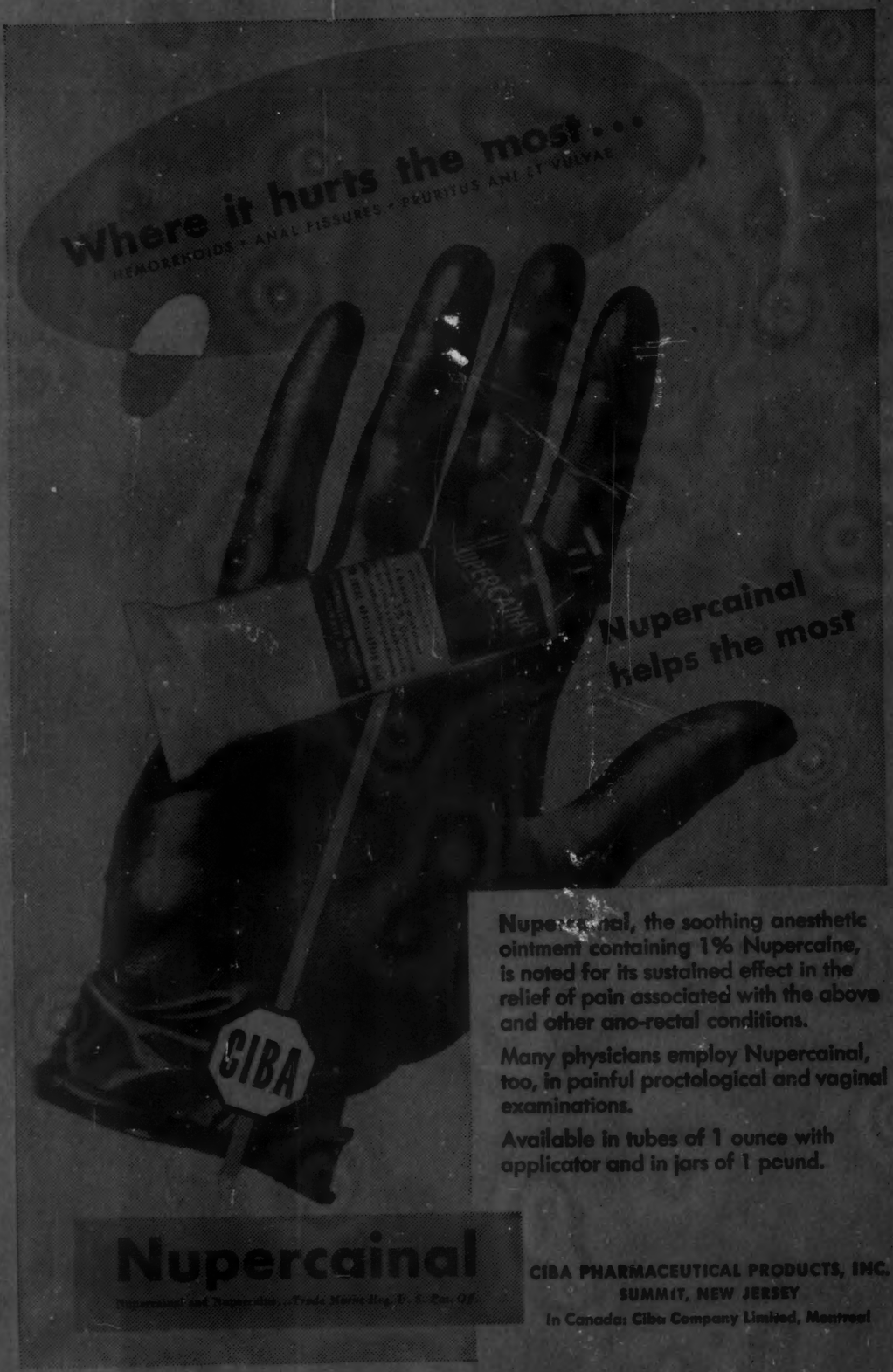

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